Comments on Commission's Proposals for Tissue Engineered Products

PROPOSAL FOR A HARMONISED REGULATORY FRAMEWORK ON HUMAN TISSUE ENGINEERED PRODUCTS: DG ENTERPRISE CONSULTATION PAPER

Fidia Advanced Biopolymers Comments

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Introduction

The present document has been prepared by Fidia Advanced Biopolymers S.r.l. (FAB), a company based in Abano Terme – Italy, active in the field of tissue engineered products and coordinator of several Research projects of the 5th and 6th European Framework Program.

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INTRODUCTION

The European Commission, DG Enterprise, published last 6th April 2004 a public consultation proposal for a harmonized European Regulation on human Tissue Engineered Products (hTEP).

FAB welcomes the Commission's initiative to consult the stakeholders, including industry, at an early stage issuing a harmonized Regulation for hTEP in Europe.

The most relevant points on the Commission's proposal we strongly support are:

- The choice of the Commission to issue a Regulation instead of a Directive
- The proposed timeframe of publication of hTEP Regulation in June 2004. This means that the Regulation could get effective at the same time as the DG Sanco Directive (2004/23/EC) is implemented into the national law
- The Lex Specialis Principle to avoid possible conflicts with other overlapping Regulatory documents

- The exclusion of xenogeneic TEP from the scope of Regulation, at least in the first edition
- Exclusion of TEPs used in non-clinical R&D studies from the scope of Regulation
- The grandfathering clause for products already on the market
- The two-tier approach for the market authorization. Although in some way artificial, the distinction between autologous and allogeneic products is clear, easily understandable and applicable
- The concept of "placing on the market" that should ensure a level playing field for all organizations working in this field

We are, on the other hand, concerned about some points in the proposal. We are summarizing them in the following list with short comments. Suggested changes and explanatory notes are reported in the text of the Proposal.

- Directive 2004/23 limits its scope for products regulated by other Directives only. This limitation should be extended to hTEPs in order to avoid a possible overlapping of two different regulatory systems
- Dual role of the EMEA as clearing house function as well as assessment body for hTEPs. The most relevant feature of an ombudsman function should be its independency from involved parties. This is strictly related to the position of the Committee that shall evaluate hTEPs
- The definition of hTEPs makes, in some extent, difficult to provide a precise and clear borderline to somatic cell therapy medicinal products. For instance, any product containing living cells exhibits metabolic activity, but this is a not relevant for the intended use of the hTEPs.
- The clear distinction of the authorization procedure for allogeneic and autologous products is partially weakened by the presence of a third class of products: Allogeneic products intended to be used for one patient only. Unless clearly explained, this could significantly affect the two-tier approach.
- The Regulation should define a clear system to guarantee a level playing field for all manufacturers regardless of the authorization procedure chosen.
- 2001/20/EC Directive on clinical trials is not appropriate for hTEPs. It must be taken also into consideration that for "traditional" tissues its application is not mandatory, and Directives covering other healthcare products (i.e. medical devices) make reference to ISO standards. This means that 2001/20/EC does not cover all products applied to patients
- Data requirements for clinical trial approval are not currently harmonized in Member States. Since multicentre, transnational studies are often considered in designing clinical investigations, this is relevant for the Industry sponsors.
- The absence of clear indications on the applicable rules for products manufactured in non-EU Countries may undermine patients confidence on the quality of hTEPs

PROPOSAL FOR A HARMONISED REGULATORY FRAMEWORK ON HUMAN TISSUE ENGINEERED PRODUCTS: DG ENTERPRISE CONSULTATION PAPER*

6 April 2004

**** This document does not represent an official position of the European Commission or its services. It serves as a tool to explore the views of interested parties on a suggested preliminary approach. The suggestions contained in this document do not prejudge the form and content of any future proposal by the European Commission.***

The proposed approach is based on consultations with, and contributions from, the expert group nominated by Member states, the European Medicines Evaluation Agency (EMEA), industry representatives as well as other experts and interested parties. It also takes into consideration the results of the public consultation held by the Commission (DG Enterprise) in 2002.

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Introduction

In 2002, the European Commission (DG Enterprise) launched a public consultation to assess the need for a legislative framework for human tissue engineering and tissue-engineered products. This consultation highlighted a fairly broad consensus, in particular amongst industry and governments, in favour of a specific and uniform EU regulatory framework covering tissue-engineered products (TEPs).

Participants in the consultation acknowledged that any new initiative should comprehensively address existing and future tissue engineered products. In particular, this should include products which currently do not fall clearly or entirely within the scope of existing legislation (such as Directive 1993/42/EC on medical devices or Directive 2001/83/EC on medicinal products).

At present, the lack of a comprehensive, clear and uniform regulatory framework creates legal uncertainties and leads to a fragmentation of the tissue engineering market: similar products are regulated differently in the various Member States, different safety requirements may apply and patients can be denied access to products which are readily available in other countries. This situation needs to be addressed as tissue engineering is an innovative and fast-moving biotechnology sector, which promises to offer a variety of new treatment opportunities for European patients.

In this context, the future proposal will aim at guaranteeing the free movement of tissue-engineered products within the Community, in accordance with Article 95 of the EC Treaty. It will take as a basis a high level of protection, as foreseen in that Article, and thus contribute to provide access to the best possible treatments for patients across the EU. Ensuring a high level of safety is paramount. The Regulation may therefore be based also on Article 152 of the Treaty (public health).

Bearing in mind the results of initial consultations, DG Enterprise has engaged in further discussions with key stakeholders and prepared the present consultation paper. This document outlines the key elements to be considered in a future regulatory proposal, with a view to receiving feedback from interested parties.

Choice of legal instrument

The choice of a Regulation, rather than a Directive or any other instrument, is a basic working hypothesis.

The future proposal should help establish an effective internal market for tissue engineered products, while ensuring the highest level of protection for patients. These products are known to present particular risks for human health due to their specific human origin, the complex processes involved in their production and their long-term implantation in the patient's body.

It is therefore essential to provide a safe, coherent and stable regulatory framework, which takes into account the specificity of tissue engineered products. In this respect, a Regulation appears to be the most appropriate instrument as it will ensure uniform and timely application of the rules, for the benefit of European patients, the industry and other actors such as hospitals and tissue banks.

FAB Comments
This choice, strongly supported by FAB, is fundamental for providing a timely and comprehensive regulatory system for these products. It is in fact important that the complete regulatory scheme for products containing or composed of human tissues and cells is put in place in an organized manner, avoiding vacancy periods.

General context

Previous consultations have indicated that many stakeholders would support a legal framework based – either partly or entirely – on a centralised authorisation procedure (involving the European Medicines Evaluation Agency - EMEA). However, they also advocate the establishment of a simple, accessible and effective authorisation procedure, which takes into consideration the specific needs of small and local actors.

Small business operators, hospitals and tissue banks often produce autologous products for local or "in-house" use. This does not mean that autologous products are produced exclusively for the local market or for internal use: tissues may be treated outside the donor's country and should therefore be able to circulate within the Community. Allogeneic products are more likely to be produced in batch and marketed in different Member States, but single applications remain possible. Although autologous and allogeneic products may carry the same level of risks, the risk of rejection is generally higher for allogeneic products. In addition, allogeneic products may present additional viral risks, since several patients may be treated with the same source materials.

Suggested approach

The cornerstone of the future regulatory framework would be a specific marketing authorisation, coupled with a manufacturing authorisation procedure. The overall proposal would be designed to ensure that autologous and allogeneic tissue engineered products can be placed on the market only if they fulfil appropriate criteria in terms of quality, safety and efficacy.

Given the general context described above, the suggestion is to establish a two-tier authorisation procedure, based on a distinction between autologous and allogeneic products. Other criteria might be proposed in the framework of this consultation, but it will always be necessary to assess whether they are workable in practice. The use of criteria such as "autologous" and "allogeneic" presents the advantage of being clear, practical and easily operational.

Thus, allogeneic products would be authorised at Community level, after scientific assessment by the EMEA, while autologous products would generally be authorised at national level, under common guidance to be agreed at European level and supervision by the EMEA. Whereas the centralised procedure would be mandatory for all allogeneic products, operators may choose to submit an application under the centralised procedure for autologous products.

The same quality, safety and efficacy criteria would apply for the authorisation of both allogeneic and autologous products. At the same time, this procedure would limit the administrative burden on many local actors wishing to produce autologous tissues. In order to further ease the burden on small operators, such as SMEs, specific incentives should also be considered (e.g. fee reduction for authorisation and scientific advice).

The main issues to be addressed in the future proposal, as well as the structure and requirements of the proposed authorisation procedure, are presented in more detail in the sections below. DG Enterprise invites interested parties and stakeholders to provide their views on this approach before 30 April 2004.

Main body of the Regulation

Scope

Proposal
- The Regulation should cover both autologous (emanating from the patient himself)

and allogeneic (coming from another human being) human tissue engineered products.

- Human tissue engineered products intended for research and development trials will be excluded from the scope of the Regulation.

- The donation, procurement and testing of cells and tissues will be done according to the rules laid down in the new Directive on setting standards of quality and safety for the donation, procurement testing, processing, storage and distribution of human tissues and cells. The Directive will guarantee the quality and safety of non-manipulated or minimally manipulated human tissues and cells, as well as the quality and safety of starting materials for substantially manipulated products (see definition below) that will be subject to the provisions of the Regulation.
- The *lex specialis* principle should apply: if a product falls under the definition proposed below, it shall be subject to this Regulation, including in case of doubts that it may also fall within the scope of other Community legislation (e.g. Directive 2001/83/EC on medicinal products for human use or Directive 93/42/EEC on medical devices).[1]

- Clearing House function: in case of remaining doubts, the EMEA should be involved in assessing whether a specific product – for which an application has been filed at central or national level (see section 3) – is to be classified as a tissue engineered product or if it does not fall under this definition. This follows the example of the FDA ombudsman in the United States.

**** Comments ****

a) General remark

The aim of this new legislation will be to provide a regulatory framework covering all human tissue-engineered products, in particular those which currently do not clearly or entirely fall under the medicinal product or medical device legislation.

b) Xenogeneic products (animal origin)

- Xenogeneic TEPs for human use may be developed in the future, meaning that there could be a need to regulate this more complex category of products. However, such products are still in their infant phase of development, so that they may be difficult to regulate at this early stage (notably due to the complex safety and ethical issues associated with them). It is therefore proposed that the future Regulation should not, for the time being, cover xenogeneic tissues intended for human use. This would not exclude the use of xenogeneic cells or tissues used for the production of human tissue engineered products, as long as these xenogeneic materials are not present in the final product. The use of such tissues and cells could be addressed in the framework of the risk management requirements.

- It is recognised, however, that the proposal should be designed to accommodate future developments in the tissue engineering sector. Consequently, it would foresee an implementation report and a possible future review of the Regulation, allowing for a reassessment of the scope of application. The opportunity to include xenogeneic tissues within

[1] By derogation to Article 2.2 of Directive 2001/83/EC, this principle would be equally applicable if a product falls both within the definition of a "human tissue engineered product" and within the definition of a "medicinal product" laid down in Directive 2001/83/EC.

the scope of the Regulation could thus be re-examined some time after its entry into force, based on a reassessment of the market situation.

c) *Borderline products*

The Regulation will seek to avoid grey areas and legal uncertainties arising from products that may be regulated by other Community legislation. Different tools will be used to achieve clarity and legal security:

- Development of a definition of human tissue engineered products, which is as precise as possible (see sub-section 2 below). This definition should be designed to encompass both autologous and allogeneic products already present on the market and those which may be developed in the coming years.

- Given the highly innovative and rapidly evolving nature of the tissue-engineering sector, it must be acknowledged that even the best possible definition will not, in itself, eliminate the risk of grey areas. The *lex specialis* principle will ensure that legal uncertainties can be minimised and that borderline products are properly addressed by existing legislation.

- If doubts remain, the "clearing house function" devoted to the EMEA will ultimately ensure that the product is classified within the appropriate legal framework.
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FAB PROPOSALS

1. It should be clearly stated that provisions of Directive 2004/23/EC for processing and distribution are not applicable to hTEPs.

2. the exclusion from the scope of the Regulation of hTEPs intended for R&D trials is substantially correct if the trials are conducted in-vitro or in animal models. Conditions for the use of TEPs in clinical trials should be part of the Regulation. To this end, a specific guidance or document should be issued defining provisions for clinical trials conduct.

3. since the ombudsman function shall be involved in product classification, a scientific evaluation shall be required. This should be managed by an independent group of specialists appointed by EMEA (e.g. a steering committee).

4. the use of xenogeneic cells or tissues in the process of preparation of hTEPs, although not intended for their administration to the patient, is in some cases mandatory to obtain the product. The demonstration that they are not present in the final product raises relevant issues because "absence" is always a relative concept. If the risk management process demonstrates that the product is safe, it should be sufficient to guarantee that any xenogeneic remnants in the final product do not arise safety concerns.

Definitions

Proposal

- "Human tissue engineered product" means any autologous or allogeneic product which:

- contains, consists of, or results in engineered human cells or tissues; and

- has properties for, or is presented as having properties for, the regeneration, repair or replacement of a human tissue or human cells, where the new tissue or the new cells, in whole or in part, are structurally and functionally analogous to the tissue or the cells that are being regenerated, repaired or replaced.

Human tissue engineered products are derived from living cells or tissues, with the final product containing viable or non-viable cells. They may, for their function, also contain cellular products, bio-molecules and biomaterials (including chemical substances, scaffolds and matrices).
For the purpose of the Regulation, human tissue engineered products can be produced as standardised products, for a limited number of patients or for a single patient. In all three cases, the products proposed in the Community will be covered by the definition of "placing on the market" (see section 3 b) below)

- *Engineering* means any process whereby cells and tissues removed from a human donor (source materials) are substantially manipulated, so that their normal physiological functions are affected.

- Autologous product: product derived from cells and tissues removed from one person and used in/on the same person.

- Allogeneic product: product derived from cells or tissues removed from one person and used in/on another person.

***** Comments *****

a) General remark

The above definition aims at including all human tissue engineered products under a single regulatory framework, while differentiating them – to the extent possible – from products that fall within the scope of other Community legislation.

b) Relationship and borderline with products covered by existing legislation

- Directive 2001/83/EC on medicinal products:

  - The structure/function-oriented definition proposed above helps to differentiate TEPs from somatic cell therapy medicinal products (Annex I to Directive 2001/83/EC focuses on metabolic, pharmacological or immunological means/action).

  - This definition may, in certain instances, overlap with the definition of somatic cell therapy set out in Directive 2001/83/EC. In this case, and depending on the final definition of tissue engineered products, the application of the *lex specialis* principle will have the effect of 'transferring' some products that could currently be considered under Directive 2001/83/EC to the new regulatory framework for TEPs. This appears as a necessary step to achieve the above stated objective to create a single, coherent and comprehensive regulatory framework for all TEPs. Indeed, in order to achieve legal

certainty, the principle should be that similar tissue engineered products fall under a single regulatory framework.[2]

- When a human tissue engineered product is used in conjunction with a medicinal product, the composite product will fall under the scope of the Regulation, since it contains engineered human cells or tissues. However, the medicinal product should also comply with the relevant requirements of Directive 2001/83/EC in order to be used in combination with the TEP (a single, integrated authorisation could be envisaged).

- Directive 93/42/EEC on medical devices:

  - Transplants, tissues or cells of human origin do not fall within the scope of Directive 93/42/EEC on medical devices (Article 1, paragraph 5, point f). The proposed definition only covers products of human origin and therefore specifically excludes these products from the scope of legislation on medical devices.

  - When a human tissue engineered product is used in conjunction with a medical device, the composite product will fall under the scope of the Regulation, since it contains engineered human cells or tissues. However, the medical device itself should also comply with the relevant requirements of Directive 93/42/EEC in order to be used in combination with the TEP (a single, integrated authorisation could be envisaged).

- Directive on standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (not yet published):

  - This recently adopted Directive covers the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells. However, when such manufactured products are covered by other Community instruments, the Directive will apply only to the donation, procurement and testing of the cells and tissues.

  - The establishment of a clear borderline between the TEP proposal and the new Directive requires that the term "engineered" be precisely defined, in order to distinguish tissue engineered products from cells and tissues covered by the Directive. The operational criterion for this distinction will be the degree of manipulation of the product, which is explicated in the definition.

  - Thus, the donation, procurement and testing of the "basic" cells and tissues (source materials) should take place in accordance with the rules laid down in the new Directive, while engineered tissues would be subject to the provisions of the proposed Regulation.

c) *Therapeutic vs. cosmetic use*

The proposed definition is broad enough to cover TEPs utilised for "therapeutic" use as well as those utilised for purely "cosmetic" purposes (e.g. cosmetic surgery). Both types of products are indeed bound to circulate within the EU. In addition, the quality and safety of a tissue engineered product is paramount, whatever the intended application of this product.

FAB COMMENTS

[2] Depending on the final Regulation, Directive 2001/83/EC might need to be adapted accordingly.

1. The definition is the core part of a regulatory document, because it is the ground for the determination of the field of application. Borderline and interpretation issues are avoided as much as the definition is clear, complete, unambiguous and flexible.
2. A simple definition of Tissue Engineered Product is not available. Several different definitions have been proposed, but none of them covers all possible products.
3. The proposal reported in the document is quite complete, but some refinement is needed.
4. The Lex Specialis principle and the proposed definition should minimize overlap with existing regulations, namely 2004/23/EC and 2001/83/EC, as amended in 2003/63/EC, Directives.

FAB PROPOSAL:

1. Definition

Proposal

- "Human tissue engineered product" means any autologous or allogeneic product which:

- contains, consists of, or results in engineered human cells or tissues and/or derivatives; and

- has properties for, or is presented as having properties for, the regeneration, repair or replacement of a human tissue or human cells, where the new tissue or the new cells, in whole or in part, are structurally and functionally analogous to the tissue or the cells that are being regenerated, repaired or replaced.

Human tissue engineered products are derived from living cells or tissues, with the final product containing viable, non-viable cells and/or their derivatives. They may, for their function, also contain cellular products, bio-molecules and biomaterials (including chemical substances, scaffolds and matrices).
For the purpose of the Regulation, human tissue engineered products can be produced as standardised products, for a limited number of patients or for a single patient. In all three cases, the products proposed in the Community will be covered by the definition of "placing on the market" (see section 3 b) below)

- Engineering means any process whereby cells and tissues removed from a human donor (source materials) are manipulated, so that the physiological functions described above are achieved.

- Autologous product: product derived from cells and tissues removed from one person and used in/on the same person.

- Allogeneic product: product derived from cells or tissues removed from one person and used in/on another person.

Explanation: the introduction of the term derivative in the definition extends the application of the regulation also to products that, as a result of the application of Tissue Engineering techniques, does not contain viable or non-viable cells. The addition should avoid debates on the term "non-viable" that might be interpreted as "non-replicating" or "dead".

3. The term "substantially" is generic and does not clearly differentiate which operations are non-substantial. If this term is used to clearly separate "traditional" tissues, regulated under 2004/23 Directive, a possible alternative demarcation could be the use of "physical" means (mincing, cutting, freezing, centrifugation, irradiation etc.), considered as non-substantial manipulation, and "non-physical" means (digestion, expansion etc.), considered as substantial manipulation.

4. Indeed, all or nearly all TEP products will have some metabolic, immunological or pharmacological mode of action, but will not have this as primary mode of action, but rather secondary or even tertiary. There is a need to clarify that tissue based substances are not medicines even though their effectiveness may be driven or aided by metabolic, immunological or pharmacological means
5. If a medical device or a medicinal product is an integral part of a hTEP, the lex specialis principle would then result in the product only requiring to be regulated under the hTEP Regulation. This does not exclude that the MD or MP component can anyway be approved according to the specific regulation.

3. Authorisation – submission and examination of applications

Proposal

No human tissue engineered product as defined in this Regulation may be placed on the market within the Community unless a marketing authorisation has been granted in accordance with the provisions of this Regulation.

This authorisation will be granted either at national level or at Community level, depending on the autologous or allogeneic character of the product:

- Allogeneic cells and tissues must receive a marketing authorisation delivered by the Community. The application dossier should first be submitted to the EMEA, which will be responsible for the scientific assessment of the product.

- Autologous cells and tissues must receive a marketing authorisation delivered by the relevant national authorities. National authorities will be responsible for assessing and authorising the autologous product. However, common guidance will be agreed at European level and the EMEA will be involved in the procedure through its network of inspectors/scientific experts. Alternatively, operators may choose to file an application under the centralised procedure in order to obtain authorisation from the Community.

*** Comments ****

a) General remark

All tissue engineered products manufactured or used in/on humans in the Community will be subject to prior authorisation, regardless of the nature of their manufacturer or their intended distribution (e.g. in-house use or marketing on a larger scale). Although the same criteria will apply for assessing autologous and allogeneic products, different authorisation procedures will be established – see point c) below.

b) Marketing authorisation

- When considering a human tissue engineered product, the 'product' is defined by a combination of product characteristics, pre-clinical and clinical testing specifications and the manufacturing process. During the evaluation procedure, all three elements would be assessed by the relevant scientific bodies as a pre-requisite for granting the marketing authorisation.

- For the purpose of the Regulation,"placing on the market" means the making available of a tissue engineered product, with a view to distribution and/or use in the Community.

- Human tissue engineered products used in research and clinical trials would not be subject to the obligations laid down in the Regulation (no marketing authorisation required).

c) *Two-tier authorisation procedure*

- Stakeholders have stressed the importance of limiting the administrative burden on small business operators, hospitals and tissue banks, which often produce autologous products for local or "in-house" use. At the same time, one needs to take into account situations where source materials are donated in one Member State and engineered in another Member State, so that the final tissue needs to be re-introduced into the initial Member State for application in the patient.

  It is therefore proposed that autologous products be assessed and authorised at national level, under the EMEA's supervision and in accordance with common guidelines agreed at European level. In order to ensure that this decentralised procedure does not hinder the free movement of autologous products, marketing authorisations delivered in accordance with this decentralised procedure would be valid for the Community as a whole.

  In addition, applicants would be given the possibility to apply for a marketing authorisation for autologous products at central level (EMEA).

- Unlike autologous tissues, allogeneic products are more likely to be produced for more than one individual patient and placed on the market in several Member States. They may present additional rejection risks as well as viral risks, which are multiplied with the number of patients are treated with the same source materials. In light of these elements, it is suggested that allogeneic products should be assessed by the EMEA and authorised at central level by the Community. A marketing authorisation which has been granted in accordance with this centralised procedure would be valid throughout the Community.

  It may be necessary to take into consideration the strong similarities between autologous tissues, on the one hand, and allogeneic tissues manufactured for a single application, on the other hand. Both types of products are characterised by single use and by the fact that they are often used at local level or "in-house". The possibility to introduce flexibility into the procedure could therefore be examined. For example, it could be envisaged to introduce a derogation whereby allogeneic products which are produced individually for a single patient (intended use) are treated in a similar manner as autologous products, i.e. exempt from central authorisation and subject to the same decentralised procedure as autologous products.

The key features of each procedure are presented in the table below. The two-tier authorisation fulfils the objectives of simplicity, accessibility and effectiveness:

- The same strict scientific criteria, in particular safety criteria, will apply for both procedures, thus guaranteeing a level playing field and equal access for patients.
- Clear and simple criteria (autologous vs. allogeneic) are used to determine where applications for authorisation should be filed and which procedure applies.
- The authorisation procedure for autologous products is easily accessible at Member State level to respond to local and in-house use.

FAB Comments

1. The application of the proposed two-tier approach, whereas tries to solve the issues for small operators preparing autologous products for their national market only, should at the same time provide a high level of confidence on all Member States. In order to have a really working system, Member States should limit the application of the safeguard clause otherwise the free movement of goods inside the Community will be greatly impaired.

2. Centralized and decentralized authorizations for autologous products should no impact on market penetration. If the centralized authorization will be considered as a “better” authorization, this will be seen as a non-competence of national Competent Authorities and will force manufacturers to apply only one of the two possible options.
3. The possibility to extend the national authorization to allogeneic products prepared for a single patient requires further clarification.
4. The therapeutic use of hTEPs manufactured outside the European Community should be regulated according to the provisions of the proposed Regulation. With regard to manufacturing authorization, special care should be taken in order to demonstrate that manufacturing operations are conducted in such a way they provide the same level of confidence required for manufacturers located in Member States.
5. Plain application of GMPs, issued to cover industrial production, to hTEPs could be very difficult due to the specific characteristics of hTEPs production methods
6. A definition of variations that require mandatory approval should be provided. For autologous hTEPs, where the variability within patients can be very high, some modifications of the method could be required to meet specifications or specifications must be sufficiently flexible to incorporate the variability.
7. Management of hTEP information should be made using only one database. The use of human cells and tissues may require the management of an additional database concerning donors and recipients, thus splitting or duplicating the data.

FAB proposals
1. The application of the safeguard clause should be in some way conditioned to the evaluation by an independent entity. This could be the same group of experts exerting the ombudsman (clearing house) function.
2. The connection between Competent Authorities and EMEA should be clearly stated in the Regulation
3. The possibility for some allogeneic products to follow the national authorization procedure should be restricted to those products in which all donated tissue or cells are used for the preparation of a product for a single patient. Single patient preparations using the same master cell bank have to be considered as standard allogeneic products
4. The grandfathering clause, to be effective, should contain also the manufacturing authorization.
5. Definition of a set of specific rules, such as FDA GTP, designed to cover all relevant aspects of the manufacturing process is needed.
6. Autologous hTEPs, where the variability within patients can be very high, are at some extent non-standardized products. Some modifications of the method could be required to meet specifications or specifications must be sufficiently flexible to take into account the possible variability
7. The manufacturing and marketing authorization for autologous hTEPs under the national procedure should be issued in all languages (same provisions as hTEPs approved through the central procedure).
8. Since the safety of a hTEPs is largely related to cells and tissues, hTEPs should be incorporated in the database used for products covered by 2004/23 Directive

ISSUE	CENTRALISED PROCEDURE (ALLOGENEIC PRODUCTS)	DECENTRALISED PROCEDURE (AUTOLOGOUS PRODUCTS)
linical testing uthorisation	Clinical testing authorisation would be granted by the competent authorities in the Member States	Similar provisions.
anufacturing thorisation	Manufacturing authorisation would be granted by the competent authorities in the Member States. The EMEA would coordinate inspections through the network of national GMP (Good Manufacturing Practice) inspectors if necessary. Good Manufacturing Practice (GMP) requirements should be the same as for medicinal product. As for gene therapy/cell therapy medicinal products, it might be unrealistic to require full GMP compliance for TEPs, e.g. when manufactured in small/academic/hospital facilities. However, it should be ensured that at least the principles of 'GMP' are met (systems should be in place). These minimum requirements will have to be defined. The Regulation should define issues related to the Qualified Person/batch release/inspections/inspection frequency. The scope of this Regulation excludes TEPs intended for research and development trials. Therefore, at the minimum, the manufacturing licences should be required for sites manufacturing clinical trial material. The main requirements for obtaining a manufacturing authorisation would be spelt out in the Regulation or in the annex. Additional guidelines would be drawn up by the EMEA.	Similar provisions. Similar provisions (it is essential to have the same level of requirements as for allogeneic products).
arketing thorisation eneral)	Marketing authorisation delivered by the Community after scientific evaluation by the EMEA. Application dossier to be submitted to the EMEA. An allogeneic product should not be placed on the market in the EU unless a marketing authorisation has been granted by the Community. The authorisation would be valid throughout the Community.	Marketing authorisation delivered by competent authorities in the Member States, under common guidance The EMEA, including its group of inspectors, would be involved in the authorisation procedure (supervision by EMEA inspectors). Similar provisions.

		Optional route for the applicant: application submitted to the EMEA and marketing authorisation delivered by the Community.
	The application should contain, amongst others, a risk analysis covering the source materials, the processing and characteristics of the product after implantation, as well as possible adverse reactions of the patient. The applicant should present a risk management programme to minimise these risks.	Similar provisions.
	The implantation of tissues should only be possible on prescription in centres authorised by the Member States (hospital environment)	Similar provisions.
ientific aluation	Scientific evaluation will be undertaken using the same principles as medicinal products, where necessary suitably adapted to the specificities of TEPs. The risk assessment component will be an integral part of this evaluation. Scientific assessment by the EMEA – a scientific body for tissue engineered products would be established (e.g. as a new Committee or as a sub-Committee of the CPMP).	Scientific assessment under the responsibility of Member States. The national member of the EMEA's scientific body for tissue engineered products should be involved in national procedures (e.g. to ensure proper training of national experts, quality assurance, etc.) However, he/she would not be obliged to participate systematically in individual evaluations. A regular information report would be provided by national members to the EMEA's scientific body. The EMEA would draw up guidelines on scientific assessment. Possibility for Member States to consult the EMEA's scientific body for scientific advice. The new body would also act as a forum for these types of consultations, which are not always linked to centralised authorisation. The body can be consulted for any scientific issue related to Tissue Engineered Products
ntent of ssier	See separate table (below).	See separate table (below).
meframe for ientific aluation	Maximum 210 days), with possible questions from EMEA to the applicant and clock-stop periods. Accelerated assessment procedure = maximum 150 days under specific conditions to be determined (e.g. major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation)	Similar provisions (maximum 210 days for standard procedure – assessment may of course take less time in practice).
lidity of arketing thorisation	General principle: five years - after first renewal, authorisation becomes valid indefinitely. Any authorisation which is not followed by placing on the market or use of the TEP within 3 years ceases to be valid. When an authorised tissue engineered product previously	Similar provisions.

	placed on the market is no longer present on the market for three consecutive years, the authorisation ceases to be valid. Possibility of conditional authorisation: subject to a requirement for the applicant to meet certain conditions, in particular concerning the safety of the product, notification of incidents relating to its use and actions to be taken. Continuation of the authorisation is linked to the annual reassessment of these conditions.	Similar provisions.
ıriations	Obligation to notify variations to the EMEA and when necessary obtain approval from EMEA. Evaluation on a case-by-case basis to determine if the authorisation remains valid. The EMEA would draw up guidelines on variations (minor vs. major) and guidelines on notification procedures.	Obligation to notify variations to the competent authorities of the Member State which granted the marketing authorisation. The EMEA guidelines on variations and notification should apply in the Member States.
ıta protection ıbridged ocedure	Follow biosimilar approach as defined in the review of Directive 2001/83/EC (authorisation protected for 8 years + 2 years until placing on the market + possible extension for 1 year)	Similar provisions.

ientific advice	The applicant may request scientific advice from the EMEA prior to submission of an application. The EMEA would draw up guidelines on procedures for scientific advice.	The applicant may request scientific advice from the competent national authorities or the EMEA. This does not create any obligations as to where the application for manufacturing authorisation should be submitted (i.e. national or central level)
ɔpeal against gative opinion	Similar to provisions in the pharmaceutical regulation: "appeal"/ "re-examination" by the EMEA - notice within 15 days – appeal within 60 days – EMEA opinion within 60 days. The EMEA would ensure the objective treatment of appeals.	Appeal to the Member State's competent authorities. Same procedure/timeframe as for centralised authorisation. Member States would set up procedures to ensure the objective treatment of appeals.
ınguages	Application: English. Summary of product characteristics (SPC), doctors' and patients' information/leaflet: in all Community languages, unless the product is marketed in limited number of countries to be specified. Content of SPC and leaflets should be defined in the Regulation. Templates would be provided by the EMEA Authorisations (Commission decision): would be published in all languages. However, the possibility to publish the annexes (i.e. authorised SPC and leaflet) in EN, FR, DE and applicant's language should be investigated	Application: Member State's language(s) SPC, doctors' and patients' information/leaflet: Member State's language(s). If translation into other languages is necessary (for the purpose of circulation within the EU or other individual MS), a draft is proposed by the authorisation holder and approved by the Member State where the product intended to be marketed. Authorisations: Member State's language.

feguard clause	A Member State can suspend the marketing of the product on his territory if it has serious	Where a Member State has serious grounds for considering that an autologous product

	grounds for considering that the product presents serious risks for patients' safety. It shall immediately inform the Commission and the other Member States of its decision and refer the matter to the EMEA. The EMEA issues an opinion. On this basis, the Commission decides whether the marketing authorisation should be suspended or withdrawn (Committee procedure – a specific Committee could be established).	authorised by another Member State presents a serious risk to patients' safety, this Member State may temporarily suspend the marketing of this product within its territory. The Member State in question must inform the marketing authorisation holder, the EMEA, and the other Member States of its decision. The Member State(s) which suspended the marketing of the product and the reference Member State should use their best endeavours to reach agreement on the action to be taken with respect to the marketing authorisation and immediately inform the other Member States of their agreement. If they do not agree within xx days, or if other Member States object to the agreed actions within xx days, the disagreeing party should refer the matter to the EMEA. The EMEA issues an opinion. On this basis, the Commission decides whether the marketing authorisation should be suspended or withdrawn (Committee procedure).
st-market rveillance/ gilance	Healthcare professionals and marketing authorisation holder: obligation to report adverse effects, product defects and any other incident to the competent national authorities. National authorities: obligation to report adverse effects, product defects and any other incident to other Member States, the EMEA and the Commission. Long term traceability of patients will have to be ensured by hospitals and manufacturers. The applicant will have to supply detailed description of the vigilance system and, where appropriate, of the risk-management system which he will introduce. Reporting guidance will be drafted.	Similar provisions.
spension/ thdrawal by e Commission the reference ember State	The Commission, after consultation of the EMEA, can suspend/withdraw the marketing authorisation (Committee procedure) if it has serious grounds for considering that the product presents serious risks for patients' safety or that it does not comply with the quality or efficacy requirements, i.e. after the safeguard clause has been used or if adverse events are reported.	The Member State which delivered the marketing authorisation (reference Member State) can suspend this marketing authorisation and the marketing of products manufactured according to this authorisation if it has serious grounds for considering that the products in question present serious risks for patients' safety. It shall immediately inform the Commission, the EMEA and the other Member States of its decision. After consultation of the relevant scientific bodies (national and/or EMEA), the reference Member State may decide to withdraw the marketing authorisation and should immediately inform the Commission, the EMEA and the other Member States of its decision. If another Member State considers that the marketing authorisation has been unduly withdrawn, it should refer the matter to the EMEA within xx days. The EMEA issues an opinion. On this basis, the

		Commission decides whether the marketing authorisation should be suspended or withdrawn (Committee procedure).
spection of anufacturing es	EMEA and Member States.	Similar provisions.

arting aterials	Donated, procured and tested in accordance with Sanco Directive (Directive on donation, procurement, testing, etc. of cells and tissues)	Same provisions.
orage and stribution	Provisions on storage and transport of source material, intermediates and finished products are part of the marketing authorisation	Similar provisions.
belling and flets	Requirements for outer packaging, patient's leaflet and doctor's leaflet.	Similar provisions.
lvertising	No advertising to the public. Requirements regarding advertisement to healthcare professionals.	Similar provisions.

tabases	Authorised allogeneic tissue engineered products would be incorporated in the Europharm database	Marketing authorisations delivered by Member States (or the EMEA) should also be incorporated in Europharm.
	Tissue Engineered Products would be incorporated in the Pharmaco-vigilance database, with different access rights (national authorities > healthcare professionals > public)	Similar provisions.
	Patients: for traceability purposes, confidential database of patients kept by each manufacturer or its representative for a minimum of xx years (New Directive on procurement, etc. of cells and tissues: 30 years). In case of a manufacturer's bankruptcy, obligation to transfer all data to national authorities of the country where the manufacturer or its representative is based.	Similar provisions.

oducts already the market on entry into rce	Grandfathering clause for products already on the market at the date of entry into force of the Regulation. Manufacturers may decide, on a voluntary basis, to seek authorisation for a product already on the market. In this event, the possibility to grant fee reductions could be considered. Competent authorities should have the right to reinvestigate such products on the basis of this Regulation, where the protection of public health so requires.	Similar provisions.

Requirements for approval – content of the application dossier

EQUIREMENTS	ALLOGENEIC PRODUCTS	AUTOLOGOUS PROCESSES
lministrative formation	*To be filled in*	*To be filled in*
eneral criteria quality, safety, icacy	General criteria/principles established in the Regulation. General criteria/principles: - Quality - Safety - Efficacy *(define key principles re clinical and non-clinical trials)*	General criteria/principles established in the Regulation. These should be as strict as for allogeneic products. General criteria/principles: - Quality - Safety - Efficacy *(define key principles re clinical and non-clinical trials)*
tailed quirements on ality, safety, icacy	Requirements on quality, safety and efficacy need to be clearly spelt out. This would be done in annex (established by Committee procedure) and further detailed guidelines drawn up by EMEA. A clear idea of annex contents needs would be given in explanatory memorandum to the Regulation.	Similar provisions (detailed requirements on quality, safety and efficacy also need to be spelt out, since risk levels are not necessarily lower than for allogeneic products).

FAB Comments
1. This table is generic and clearly requires further analysis
2. The Comitology procedure should be applied involving at an early stage all stakeholders, in order to use as much as possible the available expertise. A "theoretical" approach should significantly affect the growth of this promising field.
3. The term efficacy should be changed in "effectiveness"

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