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

DG ENTERPRISE CONSULTATION PAPER*

Consolidated Eucomed Comments

30 April 2004

Eucomed proposals are highlighted this way

The original text we want to comment or we suggest to replace is highlighted in this way

* 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.

Table of contents

Foreword

EUCOMED, welcoming the possibility to comment, given by the Commission, would like to provide these general comments

- Autologous hTEPs may be far more complex than allogeneic hTEPs which makes it very difficult for national authorities to correctly assess. In such case probably Member States will appoint existing bodies to do the assessment and these will most likely be pharmaceutical bodies. Usually these national pharmaceutical bodies have limited expertise on how to evaluate materials like scaffolds and polymers, or interactions of the cells with the materials. Such risk may be reduced but not eliminated when considering of the possibility of a new Committee for hTEP that remains a sub-committee of CPMP. This is why EUCOMED favours (a) limited Centres of Excellence for the "decentralised procedure" instead of each Member States being able to have their national assessment bodies and (b) for the "centralised procedure" a clearly and completely independent new Committee for hTEPs at the EMEA level.

-.The system considered for autologous hTEPs may be attractive for large countries where the local market is large enough (such as France and Germany), but for smaller countries (the majority of the EU), the local market alone is not sufficiently attractive. Exporting hTEPs is the only way to sustain the activity. This is why autologous hTEPs are currently largely circulating within the European Union and are also often shipped over the EU border (e.g. autologous chondrocytes). Thus both the centralized and decentralized procedures for autologous hTEPs shall ensure good and immediate recognition of their European authorization.

- Although autologous hTEPs are currently considered in this document as lower risk, no academic hospital or industry will invest in clean rooms, validated equipment and Quality systems to only treat very few patients (e.g. 5 patients per year). Thus a "relative risk" to the population may not be a valid argument. In addition, it could even be argued that producing many autologous product at the same time could impose more risks (mix-ups and cross-contamination) to all patient materials cultured at the same time as compared to some allogenic products. Perhaps some simplified procedures might be possible, provided that high level of quality and safety are maintained. In addition some allogeneic hTEPs have also limited batch size. e.g. Demineralized Bone Matrix, where the final hTEPs just come from one single donor. Finally lots of SMEs are currently preparing some allogenic hTEPs in the European Union. Thus the demarcation criteria based on autologous/allogeneic status may be difficult to implement in practice.

<u>Considering the above, Eucomed would like to propose:</u>

1) Allow the choice to all hTEPs to either go through the "centralized" or "decentralized" route without necessarily looking for a demarcation criteria that is

not needed especially if the level of expertise required for assessment is ensured for both these procedures.

2) Instead of national authorities, develop a few "Centers of Excellence", having a clearly defined scope based, for example on the route of administration of the hTEPs.

3) Such "Centre of Excellence" approval should have the same value/recognition as the "centralized" approval (via a specific independent new hTEP Committee within EMEA)

4) Eucomed strongly favors point (1) above but, if the decentralized procedure shall be limited to some specific hTEPs, the Commission should then consider instead of an absolute demarcation criteria, having an evolving list indicating which types of hTEPs could go under the decentralized route. This would be comparable to how the FDA operates today, e.g. skin product devices, DBM product devices…

5) Demarcation with medicinal products and hTEPs vs. MDD issues

Many hTEPs act with a pharmacological, immunological or metabolic function. The danger is that if EMEA has also the clearinghouse function it could possibly classify most hTEP's as medicinal products

A possible solution is a) to have the ombudsman function separate from CPMP and from the new committee and, b) to have also representatives from Industry Organizations (EUCOMED, EuropaBio, EFPIA) in the group. They should work on the classification, such that no conflicts with sensitive data arise. Companies, when in doubt, should have the possibility to contact <u>in advance</u> EMEA by submitting a Request for Designation (answer in 60 days). This is common practice in USA.

For the biomaterials component this should not require a separate CE marking (it could make the system very complex)

6) GMP + clinical trials + additional medicinal-like requirements issue

- Medicinal GMPs are in come details not applicable to hTEP (QP,implantation on prescription, SPCs no reference to ISO 13485)

- ICH GCPs are, in some details not applicable to hTEP and will not help in terms of flexibility to bring products to patients

- Evaluation time long for low risk products

<u>Proposals</u>:

- include reference to ISO 13485

- make special regulations for clinical trials with hTEPs.

- make accelerated routes possible

7) More guidance is needed on what constitutes a medicinal product as compared to hTEP

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 (HTEPs).

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). Eucomed requires clarification on this addition, since we would prefer product approvals to be under article 95 of the Rome treaty.

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.
Eucomed favours a Regulation as being quicker (i.e. no transposition) and not subject to problems encountered at the time of transposition.

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.

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.
Eucomed wants to draw the attention to the fact that several SMEs or local actors are preparing allogeneic hTEPs. Thus it is important to consider their access for these allogeneic products to the "simple, accessible and effective authorisation procedure", i.e. decentralised procedure.

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. 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 effectiveness[1].

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.

Suggested deletion of the part highlighted in yellow

It shall be considered whether an absolute demarcation criteria is needed. In effect, if the decentralised system is effective and limited to some Centre of Excellence having good expertise and working with similar guidance as EMEA, one should consider that the authorisations are equivalent in terms of validity between the decentralised and the centralised route. Thus trying to restrict the utilisation of the decentralised route appears to be no longer relevant.

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.

Suggested deletion of the part highlighted in yellow

The same quality, safety and effectiveness 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.

[1] This new wording does allow to avoid misleading interpretation since being new and not yet utilised in Health Care regulation (neither the medicinal *efficacy* nor the medical device *performance*)

MAIN BODY OF THE REGULATION

1. 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. Clarification is required: if this is intended to consider preclinical trials (i.e. non clinical application on human beings) this exclusion is acceptable; on the contrary, if this is intending to consider clinical trials, we would object as we would favour such clinical trial regimes to be included by this Regulation. In fact, we believe that all current Clinical Trial regimes are not relevant for hTEPs and we think therefore it is appropriate to define a specific regime for Clinical Trials in this hTEP 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.

Suggested deletion of the part highlighted in yellow

Directive 2004/23/EC provides derogation for products covered by a "Directive"[2], but does not refer to a Regulation. Therefore it is lagally

[2] Extract from 2004/23/EC Article 2 states: "***Scope*** *1. This Directive shall apply to 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 intended for human applications.*

Where such manufactured products are covered by ***other directives****, this Directive shall apply only to donation, procurement and testing."*

important to clarify this, so that a clear reference to the only applicable parts of 2004/23/EC are indicated in this hTEP 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 as amended on medicinal products for human use or Directive 93/42/EEC on medical devices) – All Medical Devices utilizing human tissue/cells/derivative are excluded from the scope of Directive 93/42/EEC following article 1.5.f except for those included through Directive 2000/70/EC, i.e. human plasma derivatives.[3]

- 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. EUCOMED favours this clearing house function that could be allocated to EMEA but would like a specific, transparent, rapid procedure to be defined with an appeal system if the operator does not agree with EMEA

** 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)

- hTEPs incorporating Xenogeneic materials 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

[3] 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.

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 intended to be present and active in the final product[4]. Several Human hTEPs are utilising viable or active xenogeneic materials that may remain present as "traces" in the final hTEP 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 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.

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[4] Rationale: Currently all human autologous keratinocytes that are cultivated for dermal replacement (after serious burn injury for example) are cultivated utilising irradiated murine 3T3 fibroblasts. These 3T3 fibroblasts are irradiated to lose their replication capability BUT NOT their metabolism (still "living" on a metabolic point of view). Final products of autologous human keratinocytes harvested after culture are more than likely to still contain few 3T3 cells that will die as soon as they are placed onto the patient, BUT that are definitely present in the final product ready to be marketed. These human autologous keratinocyte products should fall under the scope of this HTEP Regulation. The same is true for some antibodies utilised during the manufacture to select specific human cells that can still be present and active in the final products since they cannot be removed.

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

2. 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[5], 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 or their derivatives[6]. 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, to achieve the desired physiological functions as described above.

- 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.

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[5] How is this to be interpreted? HTEP tissue/cell or the regenerated tissue/cell after the HTEP implantation?

[6] The role of this HTEP regulation is to provide a regulatory framework for products that are not regulated today as expressed in the quoted *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*, such as human Demineralized Bone Matrix, human collagen dermal filler…

** 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

Eucomed would like to emphasise the following:

- Ø Many hTEPs may act through pharmacological, immunological or metabolic means and those hTEPs should remain in the scope of this Regulation (not Medicinal Products).
- Ø Gene transfer may be used in the process of establishing a specific cell line (Master Cell Bank) for hTEPs
- Ø There should be no requirement for CE marking of the "matrix" if the hTEP is utilising a matrix/scaffold, since the matrix may not be marketed as an individual medical device
- Ø This hTEP Regulation should cover all combination products, e.g. hTEP + MP and hTEP + MD

- Directive 2001/83/EC on medicinal products:
  - The structure/function-oriented definition proposed above helps to differentiate hTEPs from somatic cell therapy medicinal products (Annex I to Directive 2001/83/EC focuses on metabolic, pharmacological and 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 HTEPs. This appears as a necessary step to achieve the above stated objective to create a single, coherent and comprehensive regulatory framework for all HTEPs. Indeed, in order to achieve legal certainty, the principle should be

that similar tissue engineered products fall under a single regulatory framework.[7]

- 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 HTEP (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 HTEP (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 HTEP 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.

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

- 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 HTEPs 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.

3. AUTHORISATION – SUBMISSION AND EXAMINATION OF APPLICATIONS

For the decentralised procedure, Eucomed suggests the following:

Ø European Centres of Competence/Excellence

Ø Not systematically one by Member States (many Member States will lack expertise in this area, resulting in possible difficulties in recognition by other Member States)

Ø Recognition by all Member States, in a manner equivalent to the centralized procedure

Ø As described in the Foreword, the decentralized procedure should not be limited to a specific category of products.

Eucomed draws the attention also to the fact that hTEPs will be imported and exported outside the EU.

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. Eucomed suggests the concept of Centre of Excellence, as described in the foreword). 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.

If it is agreed that an approval from a local Centre of Excellence, is equivalent to an EMEA approval, then allogeneic products should have the opportunity of being authorised at this level.

Centres of Excellence should be dedicated to specific groups of products

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.

Eucomed would like to reiterate its comments as raised during the consultation meeting, i.e.:

Ø Industry expertise should be utilised as much as possible

Ø Industry and other stakeholders should be involved in the formulation of technical requirements and subsequent adaptation to technical progress

Ø The use of Risk Management procedures should be a key feature of the Regulation

ISSUE	CENTRALISED PROCEDURE (ALLOGENEIC PRODUCTS)	DECENTRALISED PROCEDURE (AUTOLOGOUS PRODUCTS)
Clinical testing	Clinical testing notification[8] to the competent authorities in the Member	Similar provisions.

[8] And not authorisation regime This system is currently well working with Directive 93/42/EEC

authorisation	States with waiting period of 60 days (this would allow the Competent Authority to react and/or raise questions if needed) Provisions for Clinical Trials should be defined in this Regulation (taking advantage of Directive 2001/20/EC and EN ISO 14155 and adapting in the light of hTEP particularities)	

Manufacturing authorisation	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[9] if necessary. Good Manufacturing Practice (GMP) requirements should be the same as for medicinal product[10]. Suggested deletion of the part highlighted in yellow As for gene therapy/cell therapy medicinal products, it might be unrealistic to require full GMP compliance for hTEPs, This is correct but at the same time this Regulation has to ensure high level of safety and aim at "a level playing field" for all operators. This is why specific GTPs should be defined for all operators with hTEPs However, it should be ensured that at least the principles of 'GMP' are met (systems should be in place). These	Similar provisions. Similar provisions (it is essential to have the same level of requirements as for allogeneic products).

[9] Training of these inspectors to the specific requirements of this Regulation is very important and should also take account of small operators (local hospitals, SMEs)

[10] We shall define specific Good Tissue Practices (GTPs) that shall take advantage from existing texts such as GMPs, EN ISO 13485…

	minimum requirements will have to be defined. Eucomed favours the specific writing of a new set of good practices, which should rather be called GTPs (Good Tissue Practices) to underline their difference from the usual medicinal GMPs and from the Medical Device ISO 13485. At the time of writing such European GTPs, the European medicinal GMPs, the ISO 13485 and the recent FDA GTPs, should be taken into account. The Regulation should define issues related to the Qualified Person Eucomed has no major objection, as long as the concept of "qualified person" is defined with sufficient flexibility (for hTEP SMEs). Adaptation from the concept of medicinal qualified person is required. /batch release/inspections/inspection frequency. The scope of this Regulation excludes hTEPs intended for research and development trials. Therefore, at the minimum, the manufacturing licences should be required for sites manufacturing clinical trial material Proposed deletion of the sentence highlighted in yellow Eucomed does not agree, since most of the validations will not be completed at this stage, especially for feasibility or pilot clinical trials. 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 with Industry representatives.	

Marketing authorisation (general)	Marketing authorisation delivered by the Community after scientific evaluation by the EMEA. Application dossier to be submitted to the EMEA.	Marketing authorisation delivered by local Centre of Excellence, under common guidance Eucomed questions this assumption, since the Centre of Excellence will have their expertise and will be working with same guidance…
	A hTEP 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.	Similar provisions. This is essential, i.e. automatic recognition by all Member States of an authorisation granted by the Centre of Excellence
	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.	Optional route for the applicant: application submitted to the EMEA and marketing authorisation delivered by the Community. Similar provisions.
	The implantation of tissues should only be possible on prescription[11] Human Demineralized Bone Matrix or Platelet Rich Plasma Gel (PRP Gel) are used by dentists. Idem for skin filler with human collagen or fibroblast, that are utilised by dermatologists, plastic surgeons, etc. Thus Eucomed would object to an authorisation regime for users since this will not be possible for independent	Similar provisions.

[11] Eucomed agrees with the prescription regime

	clinicians who will use hTEPs.	
Scientific evaluation	Scientific evaluation will be undertaken using the same principles as medicinal products. Eucomed finds difficult to accept without knowing the principles behind this statement: adaptation to the specificities of hTEPs is always required. 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 (a new specific Committee).	Scientific evaluation under the responsibility of the Centre of Excellence. The national member of the EMEA's scientific body for tissue engineered products should be involved in local procedures (e.g. to ensure proper training of 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 local Centre of Excellence to the EMEA's scientific body. The EMEA would draw up guidelines on scientific assessment with Industry Representative and taking due consideration of the paramount concept of Risk Management. Possibility for Centre of Excellence 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
Content of dossier	See separate table (below).	See separate table (below).
Timeframe for scientific evaluation	Maximum 150[12] days), with possible questions from EMEA to the applicant and clock-stop periods. Accelerated	Similar provisions (maximum 150 days for standard procedure – assessment may of course take less time in

[12] An implantable class III medical device is currently assessed by a Notified Body under Council Directive 93/42/EEC within an average time of 90 to 120 days and market experience demonstrate the quality, safety and performance of such implanted devices. It is then a matter of resource allocation rather than duration of procedure to ensure effective assessment. 150 days would then be already extremely long especially if it would have included the" Stop the Clock "system.

	assessment procedure = maximum 90 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)	practice).

- Ø Eucomed suggests utilising at the best from the current MP and MD systems especially since some combination hTEPS exists
- Ø Eucomed suggests utilising electronic submission
- Ø Eucomed suggests adapting the system to the specific environment of hTEPS operators

Validity of marketing authorisation	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 hTEP within 3 years ceases to be valid. When an authorised tissue engineered product previously 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. Similar provisions.
Variations	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	Obligation to notify variations to the Centre of Excellence which granted the marketing authorisation. The EMEA guidelines on variations and

	with relevant stake holders including Industry Representatives would draw up guidelines on variations (minor vs. major) and guidelines on notification procedures.	notification should apply by the Centre of Excellence.
Data protection – abridged procedure	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) Proposal to delete the sentence highlighted in yellow This is correct if we do not utilise cells as the driver for the definition. For example the first company to register a cell suspension of chondrocytes could automatically remove all other competitive products from the market.	Similar provisions.

Scientific advice	The applicant may request scientific advice from the EMEA prior to submission of an application. The EMEA with relevant stake holders including Industry Representatives would draw up guidelines on procedures for scientific advice.	The applicant may request scientific advice from the Centre of Excellence 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)
Appeal against negative 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. Same procedure of appeal in between EMEA and Centre of Excellence	Appeal to the Centre of Excellence. Same procedure/timeframe as for centralised authorisation. Centre of Excellence would set up procedures to ensure the objective treatment of appeals.
Languages	Application: English. ~~Summary of product characteristics (SPC)~~ ~~doctors' and patients' information/leaflet~~ Information supplied with the product (preferred term): in all Community languages, unless the product	Application: Local Centre of Excellence language(s) or English ~~SPC, doctors' and patients' information/leaflet~~ Information supplied with the product (preferred term): Centre of Excellence language(s). If

	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~~ information supplied with the product) in EN, FR, DE and applicant's language should be investigated	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: Centre of Excellence language and English.

Safeguard clause	A Member State can suspend the marketing of the product on his territory if it has serious 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).	Where a Member State has serious grounds for considering that an autologous product authorised by a Centre of Excellence 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 Local Centre of Excellence 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).

Post-market surveillance/ vigilance	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, the Local Centres of Excellence 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 Bio-vigilance system and, where appropriate, of the risk-management system which he will introduce. Reporting guidance will be drafted.	Similar provisions.
Suspension/ withdrawal by the Commission or the reference Member 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 effectiveness requirements, i.e. after the safeguard clause has been used or if adverse events are reported.	The Local Centre of Excellence which delivered the marketing authorisation 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, the other Centres of Excellence and the other Member States of its decision. After consultation of the relevant scientific bodies (local and/or EMEA), the Centre of Excellence may decide to withdraw the marketing authorisation and should immediately inform the Commission, the EMEA, the other Centres of Excellence 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).
Inspection of manufacturing sites	EMEA and Member States.	Similar provisions.

Starting materials	Donated, procured and tested in accordance with Sanco Directive (Directive on donation, procurement, testing, etc. of cells and tissues)	Same provisions.
Storage and distribution	Provisions on storage and transport of source material, intermediates and finished products are part of the marketing authorisation	Similar provisions.
Labelling and leaflets	Requirements for outer packaging, Eucomed questions the need for this requirement	Similar provisions.
Advertising	No advertising to the public Requirements regarding advertisement to healthcare professionals.	Similar provisions.

Databases	Authorised tissue engineered products would be incorporated in the specific database Tissue Engineered Products would be incorporated in the Bio-vigilance database, with different access rights	Marketing authorisations delivered by Centre of Excellence (or the EMEA) should also be incorporated in the specific database. Similar provisions.

	(national authorities > healthcare professionals > public) 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.
Products already on the market upon entry into force	Grandfathering clause for products already on the market at the date of entry into force of the Regulation Would it be grandfathering for all the EU market even though just being currently authorised in a couple of Member States and will it be restricted to these couple of Member States? EUCOMED would favour the first scenario. 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. Proposal to delete the sentence highlighted in yellow Too difficult for old products and contrary to the grandfathering concept. Member States still do have the safeguard clause in any case.	Similar provisions.

4. REQUIREMENTS FOR APPROVAL – CONTENT OF THE APPLICATION DOSSIER

REQUIREMENTS	ALLOGENEIC PRODUCTS	AUTOLOGOUS PROCESSES
Administrative information	To be filled in	To be filled in
General criteria of quality, safety, efficacy	General criteria/principles established in the Regulation. General criteria/principles: - Quality - Safety - Effectiveness (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 - Effectiveness (define key principles re clinical and non-clinical trials)

Detailed requirements on quality, safety, Effectiveness	Requirements on quality, safety and Effectiveness need to be clearly spelt out. This would be done in annex (established by Committee procedure with Industry Representatives) and further detailed guidelines drawn up by EMEA with Industry Representatives. A clear idea of annex contents needs would be given in explanatory memorandum to the Regulation.	Similar provisions (detailed requirements on quality, safety and Effectiveness also need to be spelt out, ~~since risk levels are not necessarily lower than for allogeneic products~~ see foreword).

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