Reaction on consultation on the “proposal for a harmonised regulatory framework on human tissue engineered products: DDG Enterprise consultation paper” of 6 April 2004.

The Ministry of Health, Welfare and Sport of the Netherlands

Introduction

Choice of legal instrument
The working hypothesis that the regulatory framework will be a Regulation is approved by the Netherlands.

Suggested approach
The suggested approach consisting of the obligation to obtain a marketing authorisation coupled with a manufacturing authorisation procedure in order to be allowed to put a human tissue engineered product on the market is a practical and workable system. The distinction between allogenic and autologous products which will be evaluated respectively on central and decentral level, is a clear choice. Essential is that the provisions on both authorisationprocedures are alike, in order to guarantee same levels of safety, quality and efficacy on all htep’s that enter the market.

Main body of the Regulation

1. Scope
- The Netherlands can approve of the proposal to exclude htep’s intended for research and development trials, if this means that these are put under the scope of the clinical trials directive.
- The creation of a lex specialis principle is a practical solution to create clearness under which legal regime a product should be evaluated. However, it might implicate adaptation of the definition in Directive 2001/83/EC.
- Clearing House function by a *scientific committee* of EMEA is a useful proposal.

Comments, Xenogeneic products
Products that contain xenogeneic materials are excluded from the scope of this Regulation. It might be necessary to *include* human tissue engineered products that contain non-viable xenogeneic material (such as scaffolds or matrices), which already are being used. If these products are not included, they might not be subject to any authorisation at all.

2. Definitions
In order to increase clearness in classification of products, and to prevent discussions on if a product is “substantially manipulated” or “non-manipulated or minimally manipulated”, we suggest adding an annex. Content of the annex would be a list of operations that are considered as “substantially manipulated” and a list of operations that are considered as “non-manipulated or minimally manipulated”. Examples of products and their classification can be a part of the annex.

Comment b. relationship and borderline with products covered by existing legislation
If a human tissue engineered product is a product in conjunction with a medicinal product or a medical device, the medicinal product or medical device has to comply with the relevant requirements. If a single, integrated authorisation is possible, it has to be by the authority that evaluates the tissue engineered products. However, it is important that in that case, the advice of the authority on medicinal products/medical devices on the not-htep part of the product, is not without obligations.
Not only Directive 2001/83/EC might need to be adapted, but 93/42/EEC as well because if a medical device is used in a htep, the evaluation of the medical device can not consider the final product. This implicates an adjustment of the essential requirements.

It has to be prevented that an autologous “product” that is authorised centrally as a medicinal product, can be authorised as a htep in a member state. Some kind of check should be build in the authorisation procedure.

3. Authorisations - submission and examination of applications

Two-tier authorisation procedure: it is essential that the national authorisation procedure is performed alike in all member states and that the supervision is regulated.

The Netherlands ministry of Health, Welfare and Sports can support the suggestion of introducing the possibility that allogeneic products that are produced individually for a single patient are treated in a similar manner as autologous products.

Page 12 “Marketing authorisation (general)”
It is stated that the implantations of tissues should only be possible on prescription in centres authorised by the member states (hospital environment). This is a useful provision to make sure that human tissue engineered products are only used in a clinical setting by specialists. However, it should be clear that “centres authorised by member states” are centres (hospitals, clinics) that comply with national standards and that no additional authorisation to use htep’s is necessary.

Page 13 “Variations”
It is important to set criteria on when a product is considered as a variation or belongs to a group of similar product. Instead of “notify” we suggest setting an obligation to *approve* variations.

Page 14 Languages
In addition to the proposed text on the decentralised procedure, we suggest to make an explicit obligation to translate the SPC, doctors’ and patients’ information/leaflet in the language of the member state where a manufacturer wants to put the product on the market, and of an obligatory approval of the text by the national authority. Besides the importance of having information available in one’s own language, this serves as a notification of what products are used in a member state.

Page 15 Post-market surveillance/vigilance
Long-term traceability, ensured by hospitals and manufacturers, needs to be facilitated, for example by creation of an international system.

Page 16 Databases
It is worth considering an obligatory registration in English in an international database of all marketing authorisations (by centralised of decentralised procedure) that is accessible by the authorities in all member states, so that actual information is always available.
Two-way communication is important for traceability: if a htep is produced by more then one producer, the last one needs to know how long patient records have to be kept.

Page 16 Products already on the market upon entry into force
Instead of authorisation on a voluntary basis, we highly recommend that for products already on the market at the date of entry of the Regulation, it is obligatory to seek authorisation in a period of five years. The possibility of fee reduction could be considered. It is not advisable that products on the market would never be subject to evaluation.

<u>4. Requirements for approval - content of the application dossier</u>
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<u>General comments</u>
On several places the proposal mentions the EMEA to execute tasks in evaluation of human tissue engineered products and development of common guidance. We suggest that EMEA should perform a coordinating role and to create a *scientific committee* of EMEA to perform these tasks. The scientific committee of EMEA should have a connection with the CPMP in order to guarantee that evaluation of products that might resemble (somatic cell therapy and htep’s) will be done comparably. Just as important is a connection of the scientific committee and national htep’s authorisation organisation, in order to prevent dissimilarities in evaluation.

Because of adopting various provisions of the legislation on medicinal products, there is a risk of creating inconsistencies. Special attention is needed to avoid inconsistenties.