LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Date: 5 July, 2004 Dnr:

Director Paul Weissenberg
Directorate F/DG Enterprise/European
Commission
88, rue d'Arlon
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Re. Draft Regulation on Human Tissue Engineered Products.

Sweden has got the opportunity to comment on the draft EU Regulation on Human Tissue Engineered Products. As has been seen from earlier consultations we support the work done on the Regulation. We are also positive to the pace with which the work is being done. Speed is important as we already get questions concerning clinical evaluation, quality systems and other important regulatory issues.

There is today already a significant amount of HTEPs in the markets of the European Union and United States and more products are under development. It is, however, important to be aware of that most of the products today (skin, bone, cartilage) are engineered within the Health Care system and it will be like that also in the future.

Enclosed, we offer some Swedish points of view for discussion. The comments are prepared by a group of scientific experts within the Agency.

On behalf of the Medical Products Agency,

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Medicinal products agency expert comments 2004-07-02 on: "Proposal for a harmonised regulatory framework on human tissue engineered products"

This document does not represent an official position of the Swedish Government or the Swedish Parliament. The comments, concerns and suggested approach is based on consultations with, and contributions from the tissue engineering expert group at the Medicinal Products Agency, Sweden.

1. DEFINITIONS

The proposed Regulation will be an extension to the Directive (2004/23/EC.) that covers donation, procurement, and testing steps in the tissue engineering process. Further, somatic cell therapy medicinal products are already covered in Directive 2003/63/EC. It is therefore crucial for the scope of this regulation that a clear line is drawn to distinguish these areas:

- Cells and tissues who are minimally manipulated, with no intention to alter their normal physiological functions. These processes/products are excluded from the scope.

- Cells and tissues who are substantially manipulated, with the intention to alter their normal physiological functions and where the new cells/tissues are structurally and functionally analogous to the cells and tissues that are being regenerated, repaired or replaced. This should be the main focus of the current legislation.

- Cells and tissues who are substantially manipulated, with the intention to substantially alter their normal physiological functions and where the effect is obtained through metabolic, pharmacological or immunological means. These processes/products are currently classified as somatic cell therapy (Directive 2003/36/EC).

2. FOCUS ON PROCESS

It is the tissue engineering process that delivers the final product for clinical use that can be regulated. An increased focus should therefore be put on the processes. There are several reasons for this:

- The processes should be granted market authorisation, as it is the process and not the products that can better be protected by intellectual property law. Further on, the know-how, e.g. value creation for commercial developers lies in the process.

- The final product of the process, e.g. cells and tissues, except from large scale batch produced allogenic products, will be prone to very large variations in terms of cell quantity, cell differentiation patterns etc.

- All processes must be qualified for clinical use by clinical safety and efficacy documentation of the resulting material by clinical trials.

By this approach a marketing authorisation would, by default, follow for products obtained through an approved process with its specifications.

3. A TWO-TIERED MARKETING AUTHORISATION

We are strongly convinced that the proposed two-tier procedure doesn't lessen the burden on SMEs and Health Care. Most likely it will both hamper the development of a European TEP industry and delay the access of European patients to TEP therapies.

From a risk management perspective it is more appropriate to consider how many patients that are exposed to each production lot containing material from one source. Therefore, we propose that the two-tiered procedure is modified as mentioned below.

a) Both autologous and allogeneic processes for single use could be approved for national production by the national CA - with the centralised procedure as an option.

b) Allogeneic processes for batch production should be evaluated and authorised by a centralised procedure, e.g. EMEA

4. REQUIREMENTS FOR MARKETING AUTHORISATION

It is appropriate to exclude research and clinical trials from the current legislation. However, it is unavoidable that requirements for marketing authorisation will have an influence on clinical development of tissue engineered products. It is therefore necessary to clearly define key requirements in the proposed Regulation. For detailed guidance we support the proposed mechanisms through the EMEA.

We have had a number of questions from both manufacturer and academia, and identified the following areas where lack of well defined key requirements are hampering current development:

- Quality systems: There are today two major systems – GXP and ISO. In the long perspective, it will be contra-productive to maintain different QS in closely related areas, and new actors in the field must feel confident that their investments are safe for the future. Moreover, the US has already extended their GXP system into current Good Tissue Practice (cGTP). We propose that a GXP system with an additional risk management component becomes the standard. A sufficient transition period should then be granted.

- Non-clinical studies will be needed prior to initiation of clinical trials. There are also some aspects of long-term effectiveness/durability and safety where non-clinical data might be needed for a marketing authorisation. The requirements for such studies will need harmonisation within the EU.

- Clinical qualification of a process delivering material for human use will always be needed for a marketing authorisation. When applicable, comparison to standard therapies shall be provided. This in order to drive the development of TEP by acceptance of these products through demonstrable benefit.