DG Enterprise Consultation Paper of April 6, 2004 "Proposal for a Harmonised Regulatory Framework on Human Tissue Engineered Products"

Response from Genzyme Europe

April 2004

Genzyme welcomes this opportunity to provide feedback on the European Commission's public consultation document for a harmonized Regulation on human tissue engineered products (hTEPs) in Europe, and congratulates the Commission for the work already done and the Stakeholder meeting of 16 April 2004.
Harmonized regulations in Europe for such products will over time dramatically increase the availability of innovative new therapies to patients and provide much needed assurance to the general public regarding their safety. In addition, they will create an also much needed stable regulatory climate for companies developing these innovative products, and improve Europe's competitiveness in the field of knowledge-based products. This stable climate would indeed encourage entrepreneurship in this field, thereby not only creating new therapies, but new employment as well, which may otherwise only be created outside Europe.

Based on the Commission's public consultation document of 6 April, Genzyme would like to present the following key points:

1. In order to guarantee a high level of quality, safety and effectiveness of the products and a stable regulatory climate, it is mandatory to have a **level playing field for all players**. This implies that all products are subject to the same regulations, both for manufacturing and placing on the market, for all producers in this field, whether private or public. This is the only way to ensure fair competition and the needed safety for the hTEPs, which are products which will bring innovation and benefits for patients but also products with a potential risk. Based on a risk management approach, trust and confidence need to be ensured for the field, while avoiding adverse events. hTEPs require high standards and rules at all levels, during the whole process and in the entire EU.

2. Genzyme is concerned about the proposed two-tier authorisation procedure, which is based on the origin of hTEPs, i.e. obligatory centralized via EMEA for allogeneic and centralized or national for autologous hTEPs. Allowing both centralized and national approval procedures will in our opinion inevitably lead to dual approval standards and discrepancies in the conformity assessment, mainly due to the scarcity of the expertise in this field, and will therefore go against the spirit and objective of the proposed Regulation, namely striving for an EU harmonized legislation.
   Also, the creation of two categories of hTEPs may lead this newly proposed regulatory framework to be suboptimally used. The most advanced applications may indeed be regulated as medicines, according to a strict interpretation of the definition of somatic cell therapy products per Directive 2003/83, and all other autologous products similar to what exists today. Legally there may seem more harmonisation, but in practice the two-tier approach risks to sustain a lack of harmonisation between member states. If implemented, it may also be precedent driven, so that the first to file will determine the path of all similar products (centralized or national).
   The way forward is to group the available pool of Member States' knowledge in a **centralized**

EU body, with a transparent, centralized and similar approval system for all.
A centralised approach should also optimize the reimbursement potential by the credibility of a similar, transparant approval process for all hTEPs.

3. Genzyme applauds the efforts of the Commission to develop a hTEPs **Regulation** instead of a Directive, as well as the proposed timeframe to publish the Commission's proposal for a hTEPs Regulation in June 2004. A Regulation is the only option to have the legislation enter into force at approximately the same time as the implementation of the DG Sanco Directive (2004/23/EC), ensuring appropriate and clear legislation for the concerned products.

Below are the comments from Genzyme on each of the sections proposed in the Commission's public consultation document of 6 April.

SCOPE

Clinical Trials
Genzyme favours that clinical trial rules specifically adapted for hTEPs are included in the new Regulation. The clinical trials Directive 2001/20/EC regulates medicinal products, and therefore does not automatically cover hTEPS.
In order to avoid confusion, to create a uniform and clear approach of clinical trials for these products, and since it will often be inappropriate to apply a pharmaceutical trial design to a hTEP used with a surgical procedure, Genzyme proposes specific provisions for clinical trials using hTEPs in the new Regulation.
However, in order to continue advancement of the field and to find a balance with academic research, experiments with research products which are not to be used in patients should be excluded from the scope of the Regulation.

Xenogeneic hTEPs
Genzyme supports the proposal to currently exclude xenogeneic TEPs from the scope of Regulation, as the issues (scientific, ethical and those raised by public concern) raised by the use of viable xenogeneic cells in humans are not fully understood yet.

Animal Tissue used in Manufacturing
There is one concern related to the current wording of exclusion of xenogeneic tissue from the Regulation. This concerns the use of animal origin cells in the manufacturing of hTEPs and/or as feeder layers, such as mouse feeder cells in skin cell expansion for treating severely burned patients. In such cases, the use of animal cells should not prevent the hTEP to be regulated under this Regulation. A scheme specifically focussing on safety, and potentially through a separate certification scheme for materials used during manufacturing processes should suffice.

DEFINITION

There is a need for a clearer definition of hTEPs, medical devices, gene medicinal products and human somatic cell therapy medicinal products. "Substantially" and "not substantially" manipulated will often not be sufficient to clearly distinguish them.
In addition to "metabolic, pharmacological and immunological action", used to distinguish between hTEPs and medicinal products, we propose to focus on the primary function or mode of action. Nearly all products may 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.

Tissue engineered products have as intended use the repair, replacement or regeneration of human tissue or function. This can, of course, result in subsequent metabolic, pharmacological, immunological, etc. effects, but these should not be defined as the primary mode of action. If the primary mode of action is considered, products based on chondrocytes for cartilage repair, and myoblasts for myocardium injection, would be considered as part of the hTEP category and not of the medicinal products category, as they are only restoring a previously existing function without having a new pharmacological or metabolic effect.
There may be cases of doubt with regard to primary mode of action, and there will be borderline products, which should be discussed and assessed by the "clearing house function".

AUTHORISATION PROCEDURE

We strongly doubt whether the two-tier marketing authorisation system for autologous hTEPs as currently proposed will work.
A decentralised procedure will imply that some products will be reviewed on a national basis only, and thus without the benefit of the pooled expertise at the Community level. Especially in the hTEP field, where important developments are expected to happen in the coming years, systematic use of all the available (and currently scarce) expertise is preferable. Ultimately, the objective is to provide hTEPs with the highest quality, safety and effectiveness profile for patients. We are concerned whether this can be ensured by the two-tier approach as described in the Commission's proposal.
Mutual recognition of approvals, especially for "sensitive products", have a very poor track record in Europe (e.g. GMO foods).
This situation can potentially lead to the situation that more complex autologous products will de facto be regulated as medicines, following the strict interpretation of the definition of somatic cell therapy, and the simpler products be regulated by the national route. This is not very different from the current situation, whereby safety, quality and regulatory uncertainty issues will occur. Moreover, this will also affect the reimbursement potential of the simpler products.

We would therefore strongly suggest a formal, centralized approval mechanism for hTEPs.
A separate, centralized regulatory review committee within the central Agency (EMEA), be it with the inclusion of a scientific appeal panel, composed of experts appointed by the member states (not necessarily equally representing all EU member states), would preferably be responsible for regulatory review and for categorisation of products.

The definition of placing on the market should also cover hospital products, even if used in one patient only, and they should be subject to the same regulatory principles. This is not yet fully clear from the definition as currently proposed by the Commission, which is not clearly covering all use of inhouse preparations. There remains room for interpretation and national rules can differ.
For instance, as a certain analogy with medical devices may exist in the reasoning used by the Commission, in Germany the *Medizinproduktegesetz* contains specific rules for devices produced in house (*Medizinprodukte aus In-Haus-Herstellung)*, which have to comply with the essential requirements but are not subject to the main CE-marking obligation (section 3.21 and 12, available at http://bundesrecht.juris.de/bundesrecht/mpg/index.html).
The situation risks being more complex with hTEPs. For instance, some hTEPs can be used during treatment in the hospital without permanent administration or implantation (such as hTEPs used in dialysis or similar treatments), and others may be implanted or administered in the hospital but absorbed in or transformed by the body before the patient leaves the hospital so that the analogy with orthopaedic implants is difficult. In that light we suggest to include in the definition of placing on the market the wording "or use in or on a human person".

Hospitals working on hTEPs may, due to missing regulatory expertise, prefer the national route because of "language", or more importantly "relationships". This implies direct competition, but without being subject to the same rules, leaning on the regulatory authorities, or even delivering the experts for such national approvals.

Genzyme recognises the need for a solution for academic centres and hospitals working on experimental products, and sees the need to make a distinction between products based on their phase of development. In these cases, a new experimental trial procedure may be regulated nationally, provided that the quality, and safety requirements for these products are the same as for the centrally approved products in the same phase of development. However, there should be a procedure which first asks for an administrative judgement by EMEA, and in cases of doubt the clearing house function should be used.

We would also suggest that the new Regulation provides for the creation of an orphan hTEPs category, to treat rare diseases, with specific incentives similar to those in place for orphan medicines.

It is also important that reference is made to existing regulations for GMO-based products. hTEPs could contain GMO's, so the approval system for such products should include the GMO review, as is the case for centrally approved medicines and for novel foods. If not, a double procedure would apply, which would create legal and regulatory uncertainty.

REQUIREMENTS FOR APPROVAL

Genzyme strongly believes in a new and appropriate Regulation harmonizing the requirements for clinical trials, manufacturing and marketing authorisation of innovative hTEPs in the entire EU.
In order to develop this field further, it will be essential to group all available expertise, including expertise from industry. This can be done through early communication and consultation between the central regulatory body and industry on a.o. the development plan, the scientific assessment criteria and guidelines, required clinical and clinical evidence, and clinical trial approval mechanisms.

We suggest a data protection system, similar to the one being used for medicinal products and a regime of protection of the innovator's expertise and IP, also during clinical trials (so as to avoid the copying of confidential information by review experts).

In view of the specificity of these innovative hTEPs, we suggest a fast and simple approval process, with the possibility of conditional and fast track approvals.
Conditional approval should also lead to reimbursement, because in many hTEPs additional and often costly surgical procedures are needed, and should not be seen by reimbursement agencies as a reason not to reimburse.
With regards to import, we suggest the same standards to apply for imported products as for hTEPS produced in the EU, and one standard for an Import License for investigational TEPs and customs clearance requirements, taking the short shelf lives of TEPs into account.

As for post-authorisation, it would be highly advisory to have a centralised assessment of the "materiovigilance" (adverse event reports) information.
Both allogeneic and autologous hTEPs should use only one database (e.g. EuroPHARM).
Safety reporting should be done through the existing electronic reporting tools which are also used

for medicinal products (EudraVigilance), with the same processes used for both autologuous and allogeneic hTEPs.

CONCLUSION

As we have outlined above, the main objective of the hTEP Regulation should be to obtain an effective and harmonized control mechanism that ensures that only high quality cell-and tissue-based products will be marketed and used. Therefore, the highest standards of safety and clinical effectiveness for all products need to be in place, while a pragmatic approach is also needed to guarantee availability and approvability of products, favouring pioneers instead of copiers.

Successful global commercialization of these types of products will eventually require implementation of globally consistent legislation that addresses the unique characteristics of these products to protect patient safety, ensure patient access to innovative therapies, and protect the extensive investment required from innovative companies to bring these products from the research phase to the patient.

This paper has been prepared by Genzyme Europe.
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Genzyme Corporation is a global biotechnology company dedicated to making a major positive impact on the lives of people with serious diseases. The company's broad product portfolio is focused on rare genetic disorders, renal disease, osteoarthritis and immune-mediated diseases, and includes an industry-leading array of diagnostic products and services.
Genzyme's commitment to innovation continues today with research into novel approaches to cancer, heart disease, and other areas of unmet medical need. The company's areas of expertise include cell, gene and protein therapies, drug discovery and development, surgical biomaterials, diagnostics, and genetics and genomics. More than 5,300 Genzyme employees in offices around the globe serve patients in over 80 countries.

Genzyme has more than a decade of experience in developing and manufacturing autologous cell therapy products that have been used to treat patients undergoing knee cartilage repair, or skin restoration following severe burns. These products represent the first commercial cell therapy products ever brought to market. In 2002, Genzyme announced a collaboration with the French Biotech company Myosix SARL to further develop the world's most advanced clinical program in the use of cell therapy to treat heart disease. The program is focused on stopping the progression from a heart attack to heart failure, which affects more than 20 million individuals worldwide. Genzyme has an active research program in autologous cell therapies, cancer vaccines, gene therapies and xenografts.