TEPS

TISSUE ENGINEERING PLATFORMS

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STATEMENT ON THE "PROPOSAL FOR A HARMONISED REGULATORY FRAMEWORK ON HUMAN TISSUE ENGINEERED PRODUCTS DG ENTERPRISE CONSULTATION PAPER"

COMMENTS:

INTRODUCTION:

TEPS welcomes the important initiative of the European Commission to set up a harmonised regulatory framework and it congratulates DG Enterprise on the advances that have been made in order to achieve this goal.

It supports the choice of a Regulation as a legal instrument. A Regulation will guarantee a timely EU-wide implementation of the new regulatory framework. It therefore is the best legal tool to serve the interests of the patients, of the industry and of the society.

In general TEPS favours all measures that ease and unify different processes of authorisation. Only this way a common market can be achieved.

Suggested approach

However, TEPS regards it as unfavourable for patients and the industry to make no distinction in the foreseen Regulation between autologous products for local or "in-house" use and autologous products that pass national borders. Of course it is the case that tissues should be able to circulate within the Community and often do circulate, but very often manufacturers and hospitals intend internal or local use only. As a matter of fact internal use is often the entrance gate for small start-ups into business. This entrance gate will be closed for many small companies if there will not be a special consideration of autologous HTEPs that are not created for export.

The problem lays in the equal handling of allogeneic and autologous HTEPs. According to the proposal both will require manufacturing and marketing authorisation and need to fulfil the same quality, safety and efficacy levels. The only difference in the two-tier approach is that allogeneic HTEPs require a centralised authorisation procedure, whereas autologous HTEPs can opt for national procedures. This two-tier approach is well presented and makes sense to some extent in our eyes.

Autologous products

However, it is very likely that this system will result in almost equal handling of both product types. Since there is no risk assessment of products both, allogeneic and allogenous HTEPs have to be considered almost equal apart from the fact of additional viral risk and increased rejection risk for allogeneic HTEPs. According to our understanding of the proposed Regulation this can result in the situation that a small

start-up that wants to treat a few patients in the local hospital with a very low risk level autologous HTEP has to conduct clinical trials. This will prevent scientific progress, product developments, job creation and patient treatments. The price for having a Regulation for a safer and harmonised health market would be to restrict this market for small players without any good reason to the disadvantage of the European community. Unless there is a clear exemption for low-risk, local (i.e. national) use autologous HTEPs from clinical studies in the approval requirements, TEPS asks for a 3rd HTEP group that complies to an authorisation procedure consisting only of the manufacturing authorisation.

As a matter of fact many SMEs that are now on the markets established their low-risk products at least in Germany with a manufacturing authorisation without clinical trials. No negative experiences have been made up to know in respect to patient and product safety. It is very likely that these companies and their products would not exist or would have needed significantly longer for market entry if the now foreseen Regulation would have been in place already.

TEPS therefore strongly recommends to exempt autologous HTEPs that are produced for local or "in-house" use from the requirement of a marketing authorisation that requires or might require clinical studies. It is of course clear that these products will not be allowed to circulate.

Fee reduction

TEPS asks for significant fee reductions or fee waivers for SMEs. The new authorisation processes will lead to increased bureaucracy and complexity for SMEs and will impose some burdens that they are willing to bear in order to guarantee patient safety needs and harmonise the European markets. As a matter of fact costs will increase significantly, in some cases to extends that will make it difficult for SMEs to keep their business running. Fee-waivers are therefore essential to guarantee the progress and survival of SMEs and therefore the continuous output of new therapies for the patients.

Lex specialis and Clearing House function

TEPS welcomes the application of the *lex specialis* principle and the introduction of a Clearing House function at EMEA. Both measures help to make the proposed Regulation very useful and applicable to special situations and cases.

Xenogeneic products

The comments on xenogeneic products is a little bit problematic in our point of view. We agree on the proposed exclusion of xenogeneic TEPs from the proposed Regulation but disagree to the sentence "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 application of this sentence would prevent products to be included under the scope of this regulation that for example consist of human cells on a porcine heart valve that is used in cardiac surgery for decades. We do not see any risk related to xenogeneic tissue in this example and no reason why it should not be considered under the scope of this regulation. The same holds true for collagen sponges and many more products.

Furthermore many products that are currently developed especially in urology and cardiovascular research use acellularised dead matrices such as porcine small intestine submucosa or vessels etc., because of certain advantages. For many of those materials methods have been developed to prevent porcine endogenous retrovirus (PERV) transmission and to prove the absence of PERV. The exclusion of these products from this Regulation certainly would lead to decreasing trust of patients and investors into

these products and therefore would harm the SMEs that develop these products. An exclusion would keep such products in their "infant" phase of development and this certainly cannot be the objective of a Regulation.

We therefore propose to change the sentence: "This would not exclude the use of xenogeneic cells or tissues used for the production of human tissue engineered products, if the xenogeneic cells or tissues used in the HTEPs are already on the market or if sterilised acellular xenogeneic tissues are used"

Borderline products

TEPS agrees to the comments on the relationship and borderline with products covered by existing legislation. It is important that the Regulation states clearly that in case of composite products where compliance with different Regulations and Directives is required just one authority is the contact authority for the applicant and that there will be just one authorisation procedure.

Allogeneic products

Our final comment is on the two-tier approach in principle. Since the same criteria will be used for assessing autologous and allogeneic HTEPs and in most cases similar provisions are used in the different authorisation procedures the main differences in the two processes are the contact partner for the applicant, the language and the responsibility for scientific assessment. It is difficult for us to see the reasons why an allogeneic HTEP should be handled different than an autologous HTEP in respect to the three factors: contact partner, communication language during authorisation process and responsibility of scientific assessment. We therefore would recommend to leave the applicant the opportunity to choose the national authorisation procedure foreseen in the proposal also at least for allogeneic HTEPs that are intended for local, "in-house" or national use.

TEPS hopes that this Regulation will lead to a harmonised market for HTEPs in Europe and to common safety standards. Both are in the interest of the industry and the initiative of the European Commission is on a very good way to achieve these goals. TEPS will continue to support this process and congratulates DG Enterprise for an in general well balanced proposal for a new Regulation.

Strasbourg, 30th April 2004

The Board