DG Enterprise consultation
"Proposal for a harmonised regulatory framework on human tissue engineered products"
April 2004

Summary of contributions

This document summarises the contributions made by stakeholders to DG Enterprise's web-based public consultation (closed on 30 April 2004). It also refers to comments provided in the framework of the stakeholders' conference held on 16 April 2004.

Stakeholders were invited to express their position in light of a consultation document published by DG Enterprise on 6 April 2004. This summary provides an overview of comments received by the closing date on the key issues identified in the consultation document.

1. INTRODUCTION

DG Enterprise received a total of 35 written contributions, including comments from individual companies (8), research and academic centres (7), European and national industry associations (5), policy-makers and governmental experts (4), tissue and blood banks (3), consultants and lawyers (3), medical and hospital associations (2), third country experts (1), insurance organisation (1) and chamber of labour (1).

A vast majority of respondents supported the European Commission's initiative to propose legislation with respect to human tissue engineered products. Comments were generally in favour of a regulation, rather than a directive.

2. SCOPE AND DEFINITIONS

a. Scope

- Research and development trials: several respondents stressed that the exclusion of research and development trials from the scope of the proposal would de facto exclude clinical trials. They pointed out that clinical trials for human tissue engineered products should be addressed in the framework of this proposal.

- Lex specialis: the lex specialis principle, as described in the consultation paper, was generally supported by stakeholders. It is considered as a useful instrument to avoid overlap with existing legislation and minimise the risk of grey areas for borderline products.

- Clearing house function: the principle of a clearing house function was welcomed in many of the stakeholders' comments. Some expressed concern that the EMEA would have a dual role as assessment body and clearing house, but it was generally recognised that it would be difficult to appoint another competent body for this function. It was suggested that the body in charge of the clearing house function should be distinct from the EMEA's

scientific committees for tissue engineered products and medicinal products. Stakeholders stressed that the terms of reference of this body should be well defined. Some of them requested that a decision to determine which legislation applies to a given product should be taken before clinical trials begin.

- Xenogeneic products: a vast majority of respondents agreed that xenogeneic living cells and tissues should be excluded from the scope of the proposal at this stage. However, it was often highlighted that it is impossible in practice to ensure that xenogeneic cells are not *present* in the final product. For instance, the use of xenogeneic scaffolds may result in the presence of inactive xenogeneic material in the final product. Some respondents suggested that legislation should ensure that any xenogeneic materials present in the final product are not viable.

- Cells of embryonic origin: a contribution suggested that human tissue engineered products derived from cells of embryonic origin should be excluded from the scope of the proposal.

b. Definitions

- Borderline products: many contributors insisted on the necessity to propose a definition which is as precise as possible, in order to avoid overlap and borderline issues. Different suggestions were made in this respect and are summarised below.

- Inclusion of derivatives of cells and tissues: a number of stakeholders stressed that derivatives of cells and tissues should be included in the definition of human tissue engineered products. Their objective is to address materials and products that do not currently fall under existing legislation on medicinal products or medical devices.

- Composite products: industry considered that, when a human tissue engineered product is used in conjunction with a medical device or a medicinal product, the composite product should be evaluated under a single, integrated authorisation procedure. The medicinal product or medical device part of the composite product would be assessed according to the same criteria as individual products, but verification of compliance would be done in the framework of the overall assessment of the tissue engineered product (i.e. no separate authorisation or CE marking required).

- "Structurally and functionally analogous": some respondents suggested that "structurally *and/or* functionally" analogous would be more appropriate. Indeed, the human tissue engineered product may not be a mere replacement of diseased tissues, but could be a different tissue fulfilling the same function.

- "Substantially manipulated": use of the term "substantially manipulated" in the definition of "engineered" triggered a number of comments by stakeholders. Some suggested that the word "substantially" should be deleted. Others considered that this term leaves too much room for interpretation. In this respect, it was suggested that a list of products could be drawn up, which would contain examples of minimally/substantially manipulated products. Attention was drawn to the fact that the US has established a list of 316 minimally manipulated products.

- "Placing on the market": some respondents considered the proposed definition of "placing on the market" as improper because it does not cover products manufactured and used in

the same facility (in-house use, for instance in hospitals). They stressed that there is no reason why such products should not be subject to the same rules as tissue engineered products manufactured by industrial operators. A large majority of stakeholders were of the opinion that hospitals, tissue banks and other local actors should be subject to the same rules as enterprises.

3. AUTHORISATION PROCEDURE

The suggested two-tier approach was discussed in almost all contributions.

- Autologous vs. allogeneic: the procedural distinction between allogeneic and autologous products was generally considered as a possible starting point, but many contributions stressed that it should be complemented with other relevant criteria. Thus, some respondents proposed to consider parameters relating to the composition of the cell population in the tissue, the physiological function of the tissue or the risk induced by the product in relation to its functionality. Other criteria were proposed, such as single donor (national authorisation) vs. pooled donor (central authorisation) or donor/receiver identified (national authorisation) vs. universal donation (central authorisation). Some stakeholders, recognising that no single criterion offers practical solutions, suggested taking different parameters into account and to draw up lists of products to be approved at national level or at central level.

- Choice of procedure: some stakeholders stressed that both allogeneic and autologous products may carry the same level of risk. It was therefore proposed that the applicant may always choose between the centralised procedure and the decentralised procedure, regardless of the allogeneic or autologous character of the product.

- Centralised vs. decentralised procedure: some respondents insisted on the scarce availability of scientific expertise in the area of tissue engineering and stressed the need to create and maintain confidence in tissue engineered products. For these reasons, they advocated a fully centralised procedure that would pool the expertise available in Europe and build confidence in tissue engineered products. If a fully centralised procedure proves impossible to establish, it was also proposed to create a limited number of "centres of excellence" in Europe. These "centres of excellence" would have the capacity to deliver marketing authorisations, which would be valid throughout the Community.

4. AUTHORISATION REQUIREMENTS

a. Clinical testing and clinical testing authorisation

- Clinical testing authorisation: very few comments were made on the principle of clinical testing authorisation, which seems to be widely accepted.

- Difference with medicinal products: stakeholders stressed that clinical tests for human tissue engineered products will be different from those carried out for medicinal products. It will therefore be essential for applicants to know at an early stage – i.e. before clinical tests begin – whether their product is a human tissue engineered product or a medicinal product. Directive 2001/20/EC was generally considered as a good basis for clinical trial

requirements, but it needs to be adapted to reflect the specificity of human tissue engineered products.

- Testing requirements and risk-benefit analysis: many contributions underscored that non-clinical and clinical testing requirements should depend on the risk-benefit analysis of the product. For instance, pre-clinical studies on animals may not be conclusive and randomised or blind tests may even be impossible. This means that, for each product, specific requirements may need to be established.

- Manufacturing licence and clinical trials: the consultation paper suggested that, "at the minimum, the manufacturing licences should be required for site manufacturing clinical trial material". Two respondents considered that the clinical trial stage was too early to request a manufacturing licence. It was argued that clinical trials would start even before the production plant is established.

- Import of material for clinical testing: proposals were made to apply the same rules as for material of EU origin and to grant only one authorisation for the Community as a whole.

b. Manufacturing authorisation

- Use of industry's expertise: industry representatives requested to be involved in the establishment of the requirements for manufacturing and marketing authorisations. Evaluations should be based on the risk-benefit analysis of the product.

- Authorised centres: different respondents considered that the implantation of human tissue engineered products should not be restricted to centres authorised in the Member States, for instance hospitals. The proposal should not impose any specific authorisations allowing practitioners to use human tissue engineered products.

- GMPs: Many stakeholders stressed that GMPs developed for medicinal products are not directly applicable to human tissue engineered products and will need to be redesigned. Recommendations were made to adapt these GMPs by taking into account the "Good Tissue Practice" in place in the United States, as well as ISO 9001 and ISO 13485.

c. Marketing authorisation

- Timeframe for scientific evaluation: a majority of stakeholders who expressed their views advocated a fast and simple evaluation. It was argued that the dossier would be less complex than for medicinal products. The timeframe for evaluation should therefore be less than 210 days. Different recommendations were made, ranging between 90 and 120 days.

- Fee reductions and other incentives: considering that the companies involved in tissue engineering are SMEs, many respondents requested a reduction of evaluation fees for such companies. Specific incentives, such as those offered for orphan drugs, were also requested on several occasions.

- Conditional approval: industry stressed that the possibility of conditional approval and fast-track approval needs to be envisaged.

- Variations: some respondents recommended establishing criteria to determine when a product should be considered as a variation of an authorised product. In addition, different suggestions were made, ranging from the obligation to approve variations to the obligation to notify them. It was proposed that guidelines be developed for variations; these guidelines would be identical for all products.

- Data protection: the suggestion to use the same data protection rules as for medicinal products (biosimilar approach) was generally supported.

- Imports: industry indicated that the same requirements of quality, safety and efficacy should be imposed on imports and effective control mechanisms should be established.

- Donor information: a few stakeholders requested that the donor be informed of the usage made of the tissue which they provide as source material.

d. Authorisation of establishments

- A few respondents indicated that the implantation of tissues should not be restricted to centres authorised by the Member States.

5. POST-AUTHORISATION ISSUES

- Safeguard clause: several respondents insisted on the necessity to establish strict requirements for the use of the safeguard clause, in order to avoid obstacles to the free movement of tissue engineered products.

- Vigilance: stakeholders recommended a vigilance system similar to that in place for medicinal products or medical devices. However, it is essential to ensure that this system remains cost effective, in particular for SMEs. Both allogeneic and autologous products could be listed in a central database.

- Traceability: several respondents mentioned that human tissue engineered products may require post-approval monitoring. A specific reporting mechanism should be established, taking into account the requirements for patient data protection.

- Grandfathering clause: the principle of a "grandfathering clause" for products already on the market/in use in Member States was generally accepted. However, some respondents considered that its application should be restricted, for instance by maintaining this principle only during the first five years after entry into force or by restricting the possibility to keep a product on the market without authorisation only in countries where this product has been marketed before the entry into force of the Regulation.

6. ETHICAL ISSUES

- Free donation: the principles of free donation established in the European Convention of Human Rights should be respected. They forbid any direct payment of the donor even if the companies processing the tissues make profits.

- Patient information: in case of allogeneic donation, it is considered important that the donor is informed as far as possible of the potential use of his cells, including when they are processed by private companies.

- Ownership of the cells and tissues after donation: as legislation differs from one Member State to another, it is recommended that the regulation should provide clarity on this issue.

- Traceability vs. anonymity and data protection: it is recognised that there is a need for full traceability of a product from the medical history of the donor, through to the complete processing and to the receiver years after implantation. Nevertheless, the regulation should ensure that data protection, and particularly the anonymity of the donor and the receiver, is always guaranteed.

- Clinical tests: the ethical principle included in Directive 2001/20/EC on good clinical practice in the conduct of clinical trials on medicinal products for human use should be applied, although it is recognised that the Directive may not be fully applicable to other domains.

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