Summary of responses to the Commission's 2002 consultation paper: "Human tissue and cell engineering products"

1. BACKGROUND

In November 2000, the European Parliament and the Council adopted a Directive concerning medical devices incorporating derivatives of human blood and plasma[1]. This Directive modified Directive 93/42/EEC on medical devices. At that time, the Council and the Commission agreed that devices incorporating other derivatives of human tissues should be subject to a specific directive.

The field of tissue engineering has evolved significantly in the meantime and it now seems appropriate to establish a regulatory framework in this area.

Tissue engineering is a new and rapidly developing technology, which aims at producing viable substitutes to restore, maintain or improve the function of human tissues or organs. It differs from standard therapies because the engineered product is integrated within the patient, affording a specific and potentially permanent cure of the disease, injury or impairment. Tissue engineering is very much an interdisciplinary field combining the application of principles of biosciences and engineering.

In July 2002, the Commission launched a public consultation to assess the "Need for a legislative framework for human tissue engineering and tissue-engineered products", so as to complement current rules on medicinal products[2], medical devices as well as donation and distribution of human tissues and cells[3].

2. CONTRIBUTORS

The Commission received fifty-one contributions. Many of the responses, in particular those provided by institutional bodies or industrial associations, were the result of a wider consultation.

The contributors can be subdivided into three main groups:

1. Government/public institution officials

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1 Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EEC as regards medical devices incorporating stable derivates of human blood or human plasma

2 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

3 Proposal for a Directive of the European Parliament and the Council setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Council Directive 89/381/EEC (COM(2000)816 final).
Proposal for a Directive of the European Parliament and the Council setting standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissues and cells (COM (2002) 319 final).

2. Industry
3. Researchers/experts

The Commission received twelve responses from governmental/institutional officials, including nine Member States, one European institution, one intergovernmental organisation and one international regulatory agency.

Industry, including individual companies and industry associations, sent eighteen contributions. Ten of these contributions were provided by SMEs. Three respondents were larger companies active in the pharmaceutical area. Other contributions came from three European industry associations, one European association of medical doctors and one national industry association.

The Commission also received twenty-one contributions from researchers/experts. These came from twelve research institutions, six lawyers and three individual professionals (doctors, pharmacists etc.).

All contributions provided valuable background information for the Commission's further actions in this field.

3. KEY FINDINGS

Ø **Need for a new legal framework**: industry and experts appeared largely in favour of a new legal framework for tissue-engineered products. There was no clear consensus among government and public institution officials: while a majority advocated a new regulatory framework, some proposed to use the existing legislation on medicinal products.

Ø **Definition and scope**: all respondents stressed the difficulty to define the scope of application of any new legislation. It was generally felt that, whatever the definition, there would always be grey zones and borderline products. Some contributors suggested the possibility to revise the scope of application of the directives on medicinal products and/or medical devices in order to reduce the risk of borderline products.

Ø **Xenogeneic cells and tissues**: government and public institution officials were equally divided as to whether xenogeneic cells and tissues should be covered in any new legislation. Individual companies were favourable to the inclusion of xenogeneic products in the new legal framework, while industry associations wished to address xenogeneic cells and tissues only if they are used as ancillary elements in the manufacture of human tissue engineered products. Other experts were also divided over this question.

Ø **Outline for a possible Community framework**: binding specifications, standards and guidance documents were generally seen as useful instruments. These would not be mutually exclusive.

Ø **Procedural aspects**: a majority of respondents seemed to favour centralised approval procedure, albeit for different reasons. Several government and public institution officials highlighted the scarcity of scientific expertise in their country to evaluate tissue engineered products. Industry and experts, for their part, considered that a system based on mutual recognition would not be the best option. Amongst those who favoured a centralised approach, a majority supported a role for the EMEA in the scientific approval process. However, some respondents were reluctant to involve the EMEA if this leads to lengthy examinations and important costs for business operators.

4. SUMMARY OF RESPONSES

4.1. Need for specific legislation

Questions:

Is the suggestion for a new specific legal framework, different from the medical devices and pharmaceutical products regulatory systems the preferred option? Should there be a differentiated approach between different kinds of products?

Responses from Governmental / Institutional bodies

Seven Member States and a candidate country were positive about a new specific framework, but with the caveat that great care was needed in defining tissue engineering products. Some doubted whether they could be adequately defined (see next question). The suggested fallback for those with reservations was to use the legal framework for medicinal products.

Two Member States declared that they favoured the use of the existing framework for human medicinal products for tissue engineered products.

The EMEA (Committee on Proprietary Medicinal Products) and the US Food and Drug Administration both felt that the existing framework for medicinal products should be used, supplemented as necessary by the framework for medical devices.

Responses from Industry

There was a clear consensus amongst industry in favour of a new legal framework devoted to tissue engineered products. However, there was no consensus on its precise nature. One European industry association supported a graded approach depending on the perceived level of risk to the recipient. The same position was reflected in the individual contributions of its members.

Another European Industry group supported a new specific flexible framework, which should depend on the mode of action of the product and a graded approach to risk assessment/management.

One national association supported a uniform European-wide regulatory process covering all biologics (including plasma-derived medicinal products, vaccines such as cell-based cancer vaccines and cell therapy medicinal products). Individual companies which contributed comments also held this view.

There were different views expressed by individual companies. One company favoured a specific legal framework or its integration into the medical device legislation, whereas another proposed to adapt the medicinal product legislation to cover tissue engineering.

Yet another European industry association argued that ‘gene and cell therapy products and vaccines (current and future, such as cancer vaccines and vaccines administered using sophisticated medical devices), including xenogeneic cells, shall be excluded from any new directive.’

Responses from experts, institutes, consultants, individuals

Most of the experts, institutes, consultants and others that reacted on an individual basis took the view that there is a need for specific legislation for tissue engineered products. It was felt that neither the medicinal products nor the medical device legislation covers this new field adequately. It was agreed that the goal of a new directive should be to ensure safety, quality and efficacy, with a risk-benefit assessment within a light and adaptable legal framework.

Some respondents recommended using the existing framework to avoid the development of a third framework, diverging from the two existing ones (medical devices, medicinal products), and any resulting confusion.

Respondents recommended a differentiated approach for different types of products, depending on the perception of risk.

4.2. Definition and Scope

Question:

Is the idea to cover "human BioOrgans, tissues and cells, autologous and allogeneic, both nonviable and viable, and including combined tissue/non-tissue type products that have been substantially modified by treatments, and that do not exert their effect through metabolic, pharmacological or immunological means" an acceptable basis for a legislative scheme?

Responses from Governmental / Institutional bodies

Only one respondent found the definition acceptable. The other respondents had slightly different reasons for disagreeing. Some noted the difficulties of mentioning the absence of metabolic, pharmacological or immunological effects as a criterion, as this may be difficult to discern. In addition, there were different views regarding the scope of any new framework. Some noted that the proposed definition overlapped with the definition of medicinal products. Moreover, the proposed definition would lead to very similar products being handled by separate legislation. There was concern about the possibility to propose a definition for such a rapidly evolving field. One institution suggested that human tissue engineered products represent a subset of medicinal products.

Responses from Industry

One European industry association believed that a tissue-engineered product should be defined by its primary mode of action i.e. repair, replacement or regeneration of human tissue or function. It was noted that such products might have "metabolic, pharmacological or immunological" effects, but that these were not the primary mode of action. In addition, the "degree of manipulation" should be a defining factor, rather than the "substantial modification".

Another European industry association suggested adding "principally/primarily" before the "metabolic, pharmacological or immunological means".

Responses from experts, institutes, consultants, individuals

The majority proposed that tissue engineering should be clearly defined and that the definitions of medical devices or medicinal products should be modified accordingly.

A few respondents proposed revising the definitions in existing directives, without qualifying precisely how this could be done, and some suggested the following definition: "all products having a principal intended action on the human body other than metabolic, pharmacological or immunological effects."

Question:

Would there be a need, in case a specific legal framework has to be set up, to reconsider the scope of existing legal provisions (for Medical devices, Medicinal products or others)?

Responses from Governmental / Institutional bodies

Those who wanted a new framework agreed that the scope of existing provisions may need to be modified. The extent of changes to be introduced would depend on the scope of the new framework. Medical devices legislation is considered less likely to need changing than legislation on medicinal products.

Responses from Industry

Most of the answers suggested revisiting the definition of cell therapy medicinal products laid down in Annex I to Directive 2001/83/EC, for one of these two reasons:

- these products should be a set close (or even identical) to human tissue engineered products and should be covered by the same new legislation, or
- the definition of cell therapy medicinal products is too broad and overlaps with human tissue engineered products.

Responses from experts, institutes, consultants, individuals

Respondents stated that, if a new tissue engineered materials legal framework were established, there would be a need to change the scope and use of the medicinal products and medical devices legislation. There was a view that all cell-based and cell-derived therapy should be removed from the medicinal products legislation, irrespective of the mode of action. Similarly, non-human, non-viable cell materials could be removed from the scope of the Medical Devices Directive if they fulfilled the new definition of tissue engineered products.

This group also wished to modify the definition of gene therapy medicinal products as laid down legislation on medicinal products.

Questions:

How should borderlines be defined, for instance regarding cell therapy or stem cells? Would the fact that cells have a metabolic pharmacological or immunological effect be the only criteria relevant for legislative purposes?

Responses from Governmental / Institutional bodies

There were diverging views, as some considered that one cannot differentiate between stem cells and cell therapy, while others felt that one must make this differentiation. There was concern that without care, similar products might be handled through different legislation.

Stem cells are recognised to be a very difficult issue and there was a plea to keep ethics out of any new legislation. Several respondents used the difficulties in defining borderlines to underline the need to reflect on regulating all tissue and cell engineered products within medicinal products legislation. Final engineered construct and therapeutic intent is what should determine definition, not the source of the cells.

Responses from Industry

Some considered that the main purpose of human tissue engineered products is to restore previously existing functions without displaying a pharmacological effect. In addition to "primary mode of action" and "degree of manipulation", some would add two other elements; "integration in the human body" and "physiological/systemic effect" to help defining the borderlines with other products, such as medicinal products.

Some considered that all new therapy products should be covered under the same umbrella in order to address their inherent diversity. Stem cells, when they are treated or manipulated, are regarded as medicinal products (cell therapy) rather than transplantation.

Responses from experts, institutes, consultants, individuals

It was generally accepted that a definition referring to “substantially modified tissue-engineered products which do not exert their principal intended action through metabolic, pharmacological or immunological means” seems in principle sufficient to define the borderline between tissue engineered products, on the one hand, and medicinal products like somatic cell therapies, on the other.

Question:

Should xenogenic organs, tissues and cells be partly covered in the directive, why and how?

Responses from Governmental / Institutional bodies

The responses were equally divided: half of the respondents supported the inclusion of xenogeneic products in the Directive, while the other half opposed it. Those who were against thought that xenogenic organs, tissues and cells should be subject to a separate Directive to avoid adding additional complexity to an already complex subject. Those who were in favour of addressing xenogeneic products in the Directive said that there may need to be some additional requirements for xenogenic cells, but that otherwise the same issues (especially with respect to risk) were at stake. Others felt they were already covered by the medicinal products legislation.

Responses from Industry

Two European industry associations and several individual companies thought that xenogenic organs, tissues and cells should only be covered by a new framework if used as ancillary

elements in the manufacture of human tissue engineered products. They considered that xenogenic non-viable tissues are already covered by medical device legislation. However, a number of individual companies (8) felt that there should not be separate regulatory frameworks for xenogenic compared to non-xenogenic products.

Responses from experts, institutes, consultants, individuals

There was no convergent opinion. Some respondents felt that we are too far from the reality of xenogenic products to contemplate regulation. Others felt that they should be incorporated within the same regulatory framework and some respondents pointed out that these are already defined as medicinal products.

4.3. Outline for a possible Community legal framework

Question:

Is there a role for European standards in support of a future legislative scheme, for instance regarding quality assurance?

Responses from Governmental / Institutional bodies

Those who could support a new framework replied positively – for both the process and the product. It was recommended that those standards should mainly concern good manufacturing practice and quality insurance.

Responses from Industry

There was a consensus in favour of introducing a body of "harmonised essential requirements" in the new legislation, based on a risk assessment approach covering quality assurance, manufacturing practices, microbiological/viral safety aspects and ethics. However, two European industry associations emphasised that it is currently premature to define standards prior to the finalisation of the marketing authorisation and the approval structure for these products. Several companies emphasised that some existing standards are not adapted to human tissue engineered products.

Responses from experts, institutes, consultants, individuals

Most of the answers were positive. It was argued that a certain number of harmonised standards relating to the generic issues of quality insurance systems, sterilisation, risk management, labelling, etc. should be developed specifically for human tissue engineered products.

It was noted that standards should not be agreed in isolation, but in co-operation with ISO and other international organisations.

The respondents who opposed the use of European standards argued that a system using standards would entail a lot of bureaucracy and would be too static for such a rapidly evolving area.

Detailed rules adopted by Committee procedures were presented as an alternative to standards. This could be a way to develop specifications for products.

Question:

Would guidance documents in support of a future legislative scheme have to be developed by authorities?

Responses from Governmental / Institutional bodies

Governmental/Institutional bodies were unanimously in favour of having supporting documents, in order to make it easier to interpret and use the directive. Even officials in favour of including tissue engineering in the framework of medicinal products (no new specific legislation) support the development of such guidance documents.

Responses from Industry

European industry associations and their individual members were in favour of guidance on specific aspects: delineation of borderlines; ethics; review process at Member State level, if any; vigilance and traceability. They stressed that documents should be developed at a central level (Commission often quoted) and not devolved to Member States.

Responses from experts, institutes, consultants, individuals

All were in favour of guidance documents as a way to react rapidly to changes. It was considered to be much quicker than standardisation or amendment of directives or their annexes. It was recommended that those guidance documents should be drafted by a group of experts regrouping research centres, universities, manufacturers and lawyers.

Some proposed that the scope of application of these guidance documents cover the areas of quality assurance, risk management, quality, control, microbiological safety of donation, production and processing practices, product performance, including preclinical studies, pre-market clinical studies and post-market evaluation.

Question:

Is there a potential need for complementary binding specifications, adopted by the Commission in co-operation with Member States?

Responses from Governmental / Institutional bodies

Most respondents answered positively, although some of them expressed reservations that the area might develop too quickly for binding specifications. There is a need to strike a balance between the necessity to respond quickly to technological change, in order to avoid hampering innovation, and the necessity to ensure safety.

Responses from Industry

One European industry association and two of its members which participated in this consultation were strongly opposed to any fixed technical specifications.

Another European industry association and some of its affiliates favoured the adoption by the Commission of ancillary binding texts easily adaptable to take account of technical progress. Some members dissented from this view.

Responses from experts, institutes, consultants, individuals

Legally binding specifications adopted by the Commission in co-operation with the Member States were generally opposed, at least at this stage of development.

Question:

Are these instruments mutually exclusive, or can one envisage them being applied to different and distinct aspects?

Responses from Governmental / Institutional bodies

All governments and institutional bodies considered that the instruments are not mutually exclusive.

Responses from Industry

One European industry association and some (but not all affiliates) thought that they should be mutually exclusive in order to provide clarity for industry. Another European industry association believed that they are not necessarily mutually exclusive because the functions they perform are very different.

Responses from experts, institutes, consultants, individuals

Only a few respondents expressed an opinion on this point. Their view was that these instruments are not mutually exclusive, since they can be applied to different and distinct aspects. One instrument or the other could be applicable depending on various factors, such as the level of risk implied by the production process.

Question:

Are the provisions on clinical tests for new biological medicinal products (approval to start the clinical trials) appropriate?

Responses from Governmental / Institutional bodies

Reactions were very diverse. Four Member States officials replied positively, two gave a non-committal response. Others replied positively but with reservations, or recognised that provisions were needed on this aspect while considering that Directive 2001/20/EC was not appropriate.

Responses from Industry

The answers were divided in two groups:

The first group, including one European industry association, believed that Directive 2001/20/EC could be extended to human tissue engineered products provided that distinction from cell therapy medicinal products is clearly established.

The second group, including another European industry association, emphasised that Directive 2001/20/EC applies to clinical trials on medicinal products for humans and therefore many of the requirements of the directive cannot be applied to human tissue engineered products. Nevertheless, several principles of this Directive could be incorporated into the requirements for clinical trials for human tissue engineered products, for instance via a European standard.

Responses from experts, institutes, consultants, individuals

The need to obtain an approval before starting clinical trials was generally supported. Some participants recommend avoiding this for autologous products as they feel the risk related to these products is minimal.

4.4. Authorisation and market access

Under this heading, the Commission invited comments on whether an approval scheme could be based on:

- a two-stage approval system, distinguishing between the licensing of the production plant, and market approval of the product, or
- an integrated quality system, in which the market access of products would be based on the company's quality system in relation to specific products and a specific assessment of that particular product.

Questions:

Are the two approaches mutually exclusive? Which one is to be preferred from the safety and policy point of view?

Responses from Governmental / Institutional bodies

There were diverging opinions, but a majority preferred a two-stage approach. Two stated that the integrated approach was better for patient safety, whereas six preferred the two-stage approach.

Responses from Industry

There was no consensus amongst industry on this issue. One European industry association and most of its affiliates were rather in favour of a two-step procedure (not mutually exclusive). The other group of European industry considered them to be mutually exclusive.

The views expressed included safety concerns about a company placing on the market a range of similar products under a single Quality Assurance certification, the need for a quality system applied both to the entire facility and the specific product. There was a preference for licensing of the production plant plus market approval (as for medicinal products) if a therapeutic claim is made. A second option (quality system plus specific assessment of the product) was suggested if there is no therapeutic claim.

Responses from experts, institutes, consultants, individuals

The "two stage approval system" and the "integrated quality system" were considered to be mutually exclusive to avoid uncertainties.

There was no consensus as to which approach should be preferred from a safety point of view (three respondents were in favour of two steps, four were in favour of an integrated system, two regarded the systems as equivalent, others had no opinion)

The group favouring the two-step approach argued that it ensures sufficient safety and would be a practical solution that could be based on the experience made with existing legislation. They argued that the rules for an integrated approach will have to be developed from scratch and that this would take too long.

The group favouring the integrated procedure argued that it offers a higher degree of safety for the patient. Some considered that this higher level of safety achieved by the "integrated approach" comes from the evaluation of the whole "company quality system" in contrast with the "licensing of the production plant separately".

4.5. Procedural aspects of the evaluation process

Under this heading, the Commission invited comments as to whether

- An application for market access would be submitted to a national authority. The national authority would prepare a draft, to be submitted to an advisory committee made up of representatives of Member States. The opinion of this committee would be sufficiently authoritative for the national authority to which the application was introduced to accept it as a basis for its decision providing access to the Community market.

- The application would be submitted to a central body/authority responsible for both evaluation and approval. This body would be composed of representatives of Member States

Question:

Is one of the options set out to be preferred?

Responses from Governmental / Institutional bodies

Five Member States officials preferred the centralised approach with an agency developing the needed expertise. Another stated that he could conceive to have centralised and decentralised procedures for different products. One was opposed to a centralised system. The officials of two Member States presented diverging opinions and two preferred not to comment at this time.

Responses from Industry

Two categories of respondents could be distinguished:

- One European industry association declined to choose between the two proposed systems. Some of its individual affiliates, however, preferred the centralised procedure.
- By contrast, the other group preferred a formal European centralised approval system. Proponents of the centralised approach system justified their position by underlining the absence of trust in a mutual recognition system and the need to harmonise requirements, practices and post-authorisation controls (vigilance, inspections).

Responses from experts, institutes, consultants, individuals

A majority was in favour of a more centralised system for reasons of open access throughout the whole Community and due to the need for a level playing field. Authorisation by a "central body" should be rapid, non-bureaucratic and should not favour larger companies in comparison to smaller ones.

The proponents of a national authorisations system stressed the simplicity and transparency of such a procedure, as well as the possibility of direct contact while the system is developing.

Question:

If an agency becomes involved, should a separate agency be created, or could the competencies of EMEA be extended?

Responses from Governmental / Institutional bodies

One official preferred not to comment. Other respondents were of the opinion that if an agency becomes involved it could be the EMEA. Two of them felt that it could be the EMEA or a separate agency.

Responses from Industry

The majority supported the concept of a central agency. Whether this should be the EMEA appeared to depend on experience or familiarity with the EMEA and its functioning. One European industry association supported the EMEA whereas the other did not support a role for the EMEA, although it accepted the idea of a European Agency.

All noted that it would be important for the central agency to have access to the appropriate expertise. Some small companies appeared wary of a centralised agency, and in particular of the EMEA: they preferred a notified body as a centralised agency.

Responses from experts, institutes, consultants, individuals

Not all respondents answered this point. Amongst those who supported a new legal framework, most favoured a centralised body. About half of them were in favour of extending the competencies of the EMEA. Several others did not express a preference between the EMEA or a new separate body. Only one respondent, among those who favoured a centralised body, said that it should be separate from the EMEA.

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