DG INTERNAL POLICIES OF THE UNION

Policy Department: Economic and Scientific Policy

Proposal for a Regulation of the European Parliament and of the Council on Advanced Therapy Medicinal Products and amending Directive 2001/83/EC & Regulation (EC) No.726/2004 (COM(2005)567)

(IP/A/ENVI/OF/2005-053)

Briefing Note

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Executive Summary

The new proposal is concerned with what are called advanced therapies; these include gene therapy, somatic cell therapy and tissue engineered products.
The products for gene and somatic cell therapies have already been classified as medicinal products and as such are regulated in the Community. However, products derived form tissue engineering are, at present, outside the Community's legislative framework. The proposed approach is based on a single, integrated regulatory framework for all advanced therapy products.

The focus is based on three levels:

1. A general Regulation on Advanced Therapy Medicinal Products, which lays down tailored regulatory principles for the evaluation, marketing authorization, post-authorization vigilance, traceability, etc.

2. Technical Requirements.
3. Detailed Guidelines.
   The use of a hierarchy of procedures seems sensible. This intention needs to be followed through by making the detailed technical requirements specific and appropriate to the nature of the products and the procedures.

The main elements underlying the ATMP proposal are:

1. The three kinds of advanced therapies are covered by the Regulation, based upon the pharmaceutical legislation, however taking into account their specific characteristics. But the actual proposal, by referencing medicinal legislation with only minor changes and without clear differentiation between products does not sufficiently take into account the specific character of tissue engineered products. And in how far it will be done in the amendments that will be elaborated by the Commission is actually not clear.
2. The ATMP-products are submitted to a compulsory centralized procedure for the marketing authorization. Within the EMEA, the Committee for Medicinal Products for Human use (CHMP) holds the responsibility for drawing up an opinion on marketing authorization to be transmitted to the Commission. This opinion is taking into account the advise of the specific Committee for Advanced Therapies (CAT), set up by the ATMP proposal.
3. Manufacturers and public authorities shall organize a post authorization monitoring of patients and products. Article 16 of the proposal for the Regulation describes, very precisely, the objective to be achieved, but says nothing of the means to do so. It not consistent to establish aims, yet not establish the means. The only real possibility of effectively carrying out traceability is by establishing a general requirement, through a latest relevant technologies procedure that can be implemented from the taking of the starting materials until their application to a specific patient. Particular attention shall be given to define the borderline, in particular, between Tissue Engineered Products and medical devices.

To handle gene and somatic cell therapy products and tissue-engineered products in the same regulatory framework is in general terms acceptable in as far as the specific characteristics of the different products are duly taken into account when elaborating the relevant specifications for each category.

The provisions applicable for clinical trials and post marketing vigilance of products are those applied for medicinal products. Here again, many requirements are not applicable for human tissue engineered products and need major modifications. Guidance documents are very useful but should not replace mandatory requirements.

Many amendments will be necessary to take into account the specific character of the TEPs. Some need to be introduced in the ATMP proposal itself, while others shall be part of the adaptations of referenced directives by the Commission.

The incentives at Community level set out in the Proposal for the Regulation are appropriate.

Contents

1. INTRODUCTION

The proposal for regulation refers to what are called advanced therapy products comprising gene therapy, somatic cell therapy, and tissue engineered products.

Gene therapy will provide innovative therapies for a number of orphan and common diseases. As gene therapy products have divergent and very special characteristics different from those of many other biological medicines, it will be appropriate to regulate gene therapy products under the umbrella of advanced therapy products together with genetic vaccines, cell therapy and tissue engineered products.

Gene therapy products are considered biological products. Investigational clinical trials in humans with gene therapy products are subject to the general requirements for drugs and biologics.

Human cells, tissues, or cellular or tissue-based products are articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

Tissue engineering has been defined as the application of the principles of life sciences and engineering to develop biological substitutes for the restoration, maintenance, modification, improvement, or replacement of tissue or organ function. In this context, Tissue Engineered Products (TEPs) include a broad range of products. The development of new and different product-specific issues are expected.

The field of Tissue Engineering is emerging as a multidisciplinary scientific effort to generate new tissues for all fields of reconstructive surgery.

There are a limited number of commercialised products in Europe. Expectations, however, are high. The market growth is expected to be substantial.

Overall positive effects can be expected, laying the foundation for further advance of tissue engineering[1].

1.1 Legal Basis and Procedure

The text of the proposal is based on Article 95 of the EC Treaty[2], to ensure the free movement of goods. The proposal also includes the regulation of market authorization of the medicinal products falling within the coherent ensemble of advanced therapies, through the European Medicines Agency's centralized procedure, regulated by Regulation (EC) n° 726/2004 [3]. As the new proposal has the double aim of achieving the free movement of medicinal products belonging to the advanced therapy group and, at the same time, to regulate the centralized authorization system, *the legal basis of Article 95 of the Treaty is necessary but not sufficient.*

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[1] Clarifying note on the presentation of the text: The document has been divided as much as possible into chapters and epigraphs, adjusting most closely to the proposal, in order to easily locate the brief evaluation comments and the possible modifications to be introduced in the form of amendments.
The paragraphs in italics emphasize the essential points on which the analysis is based on which a possible amendment can be drafted, which text is underlined.

[2] Article 95, which establishes the co-decision procedure described in Article 251, is the legal basis for achieving the aims set out in Article 14 of the Treaty, which includes the free movement of goods (Article 14(2), in this case advanced therapy medicinal products for human use.

[3] DO L 136 de 30.4.2004, p. 1.

Since it is going to modify the Regulation (EC) n° 726/2004, which establishes community procedures for the authorization, control and pharmacovigilance of medicinal products, for human and veterinary use, as well as the functioning of the European Medicines Agency, the new Proposal must also be based, "Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof, and on letter b) of sub-section 4 of Article 152."[4] which was the legal basis for the creation of the Agency. This deficiency in the legal basis should be rectified during the parliamentary passage of the Proposal.

1.2. Legislative and administrative simplification

The proposed approach is based on a single, integrated regulatory framework for all advanced therapy products. The focus is based on three levels:

1. A general Regulation on Advanced Therapy Medicinal Products, which lays down tailored regulatory principles for the evaluation, marketing authorization, post-authorization vigilance, traceability, etc.
2. Technical Requirements.
3. Detailed Guidelines.

1.2.1. The Regulation

We have before us a Regulation that aims to establish a single integrated framework; this would require a codification of the whole sector. In practice, however, it does not do this, it refers to other Directives, so that legislative transparency and simplification remain only a desideratum. *At least, the proposal should be amended to indicate more clearly which parts of the referenced Directives and Regulations apply.* Possibly progress in this direction can be made in the parliamentary sphere, incorporating the fundamental demands to straightaway carrying out the Commission's objective of formal codification[5] of the Directives that regulate the distinct groups of medicinal products that fall under the heading of advanced therapies.

1.2.2. Technical Requirements.

The requisites for gene therapy and somatic cell products have already been laid down. [6]. A similar approach is proposed for tissue engineered products, i.e. the Commission will establish the main technical requirements that are specific to these products in Annex I to the Directive 2001/83/CE and further complement them with guidelines.

1.2.3. Detailed Guidelines.

Thus, the guidelines already approved for gene and somatic cell therapy will remain in force, and similar guidelines are proposed for tissue-engineered products.

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[4] Possible amendment to introduce in the first paragraph of the preamble of the Proposal.

[5] Possible amendment for to introduce in the Article 2 (4):
"For the future development of the regulatory environment it needed to have at EU level a codified document available where all relevant legal texts relating to ATMP are combined".

[6] See Annex I of Directive 2001/83/EC (Directive modified by Directive 2003/63/EC (DO L 159 of 27.6.2003, p. 46). (modifiable by 'comitology')and completed through guidelines (See http://www.emea.eu.int/htms/human/itf/itfguide.htm.)

1.2.4. Common specifications to be utilized

The text of the Proposal records and makes reference to the directives that affect the sector and that have to be modified, with specific specifications for advanced therapies. This revision of the existing directives and guidelines should also facilitate the differentiation and characterization of the different, not always identifiable products, with the general generic definitions.

1.2.4.1. The requirements of quality and safety for donation, procurement, and testing, of human tissues and cells will be those set out in Directive 2004/23/EC[7].

1.2.4.2. Clinical trials of advanced therapy medicinal products must be carried out in accordance with Directive 2001/20/EC[8]on the application of good clinical practices in the making of clinical trials[9]. Some of the required changes are so fundamental that they need to be at least identified within this Regulation.

1.2.4.3. The detailed guidelines of good clinical practice for ATM products undergoing trials for human use shall be established, while the requisites to authorize the manufacture or importation of such products will follow Directive 2005/28/EC[10], appropriately modified.

1.2.4.4. The manufacture of advanced therapy medicinal products must correspond the principles of correct manufacturing practice. The Proposal should explicitly allow either a GMP approach established in Directive 2003/94/EC[11] or a Quality Assurance system certification approach specified in Directive 93/42/EC Annex II (see point 3.1.1).

1.2.4.5 Advanced therapy medicinal products can incorporate medical devices or active implantable medical devices. These devices also fulfill the essential requirements laid down in Directive 93/42/EEC[12], relating to medical devices, and in Directive 90/385/EEC relating to active implantable medical devices[13].

1.2.4.6. Manufacturers and public authorities shall organize a post authorization monitoring of patients and products.

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[7] DO L 102 of 7.4.2004, p. 48.

[8] DO L 121 of 1.5.2001, p. 34.

[9] Possible amendment for to introduce in the Article 4 (2):
"In addition, Directive 2001/20/EC need to be reviewed, since some articles may need to be amended to take characteristics and requirements of TEPs into account".

[10] DO L 91 of 9.4.2005, p. 13.

[11] DO L 262 of 14.10.2003, p. 22.

[12] DO L 169 of 12.7.1993, p. 1. Directive last modified by Regulation (EC) nº 1882/2003 of the European Parliament and Council (DO L 284 of 31.10.2003, p. 1).

[13] DO L 189 of 20.7.1990, p. 17. Directive last modified by Regulation (EC) nº 1882/2003 of the European Parliament and Council (DO L 284 of 31.10.2003, p. 1).

1.3. Scope

As has been said, the new proposal is concerned with what are called advanced therapies; these include gene therapy, somatic cell therapy and tissue engineered products.

The products for gene and somatic cell therapies have already been classified as medicinal products and as such are regulated in the Community [14]. However, products derived form tissue engineering are, at present, outside the Community's legislative framework. The new Proposal for Regulation intends to regulate those specifically derived from tissue engineering and also to create a single, integrated framework for the three groups of products that fall under the denomination of advanced therapies. At the same time as the sector of advanced therapies is defined and harmonized, the Regulation regulates the marketing authorization procedure and determines the centralized procedure through the Agency, creating a new scientific committee called the Committee for Advanced Therapies (CAT), which will work closely with the Committee for the Evaluation of Medicinal Products for Human Use, in a complex system which is set out in the Proposal for the Regulation.

To handle gene and somatic cell therapy products and tissue-engineered products in the same regulatory framework is in general terms acceptable in as far as the specific characteristics of the different products are duly taken into account when elaborating the relevant specifications for each category.
But, *the actual proposal, by referencing medicinal legislation with only minor changes and without clear differentiation between products does not sufficiently take into account the specific character of tissue engineered products.* And in how far it will be done in the amendments that will be elaborated by the Commission is actually not clear.

1.4. Exclusions

The new Proposal, unmistakably and repeatedly, is directed to regulating the three groups of advanced therapy products, (i.e. those products intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process), by bringing them within the global scope of the pharmaceutical legislation [15].

The proposal explicitly excludes from the scope of this regulation products made on a one-off basis by a non-industrial manufacturing process. Tissue engineering products entirely processed in tissue banks (hospitals) should not be requested to follow the centralised procedure. However, the regulation should cover all products (whether or not industrially manufactured), but clearly stating that for products made on a one-off basis by a non-industrial manufacturing process the centralised procedure would not be compulsory.

This Regulation does not apply to any Advanced Therapy Medicinal Product (ATMP) intended for research and development trials.

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[14] Directive 2004/23/CE, which establishes norms of quality and safety for human tissues and cells (DO L 102 of 7.4.2004, p. 48.). It should be remembered that these norms apply to donation, procurement and evaluation of human tissues and cells that contain advanced therapy medicinal products. Regulation (EC) n° 726/2004, which lays down the so-called 'centralized procedure' and the function and structure of the European Medicine Agency (EMEA, hereafter 'the Agency');
– Directive 2001/83/EC on medicinal products;
–Directive 93/42/EEC of the Council, relating to health products (DO L 169 of 12.7.1993, p. 1.), and Directive 90/385/EEC of the Council on active implantable medical devices (DO L 189 of 20.7.1990, p. 17).
Part IV of Annex I of Directive 2001/83/EC, modified by Directive 2003/63/EC, DO L159 of 27.6.2003, p. 46. See also the 'Communication of the Commission on Community Proceedings for the authorization of marketing of medicinal products, DO C 229 of 22.7.1998, p. 4.

[15] Article 2(1) of Directive 2001/83/EC. DO L 311 of 28.11.2001, p. 67.

Therefore, all industrially manufactured ATMPs are included in the Proposal. There remain excluded from the scope of the Proposal those ATMPs prepared as *Magistral formula*[16]. No mention whatever is made of *Official formula*[17], although these can play an important role in hospital practice.

This omission should be corrected when the Proposal is brought before Parliament. Not to do so would leave a serious lacuna in the legislation. Any advanced therapy medicinal product, which is both prepared in full and used in a hospital, in accordance with a medical prescription for an individual patient, need to be in accordance with a production process specified to that identified patient.

A new paragraph must be added to indicate that "Magistral and Official formulas do not have to follow all the procedure to obtain the centralized authorization of the Agency (EMEA). However, all the requirements established to guarantee quality, safety and efficacy must be enforced, and therefore, they must be subject in their preparation to good manufacturing practices and the other demands set out in the technical directives and guidelines"[18].

Where some exception is needed, for example, a medical prescription for an individual patient and used in the hospital itself, would be indicated in the guidelines drawn up by the Commission.

All (including hospitals) routine treatments/products must follow the ATMP regulation. The regulation should only not apply to treatments, products and processes that are used for research purpose or on exceptional basis (one-off basis).

We need to ensure that ATMPs used by practitioners in their treatment of patients are in compliance with applicable regulations, including regulations designed to prevent the transmission or spread of communicable disease.

1.5. Objectives

The aim is to harmonise legislation in the EU and to enable a common European market, while safeguarding patient protection. Its goal is to ensure hTEPs are of high quality, safe and effective, and by overcoming national differences, to lay the foundations for a single Europe-wide market for these products.

The regulation aims at attaining the general objectives of the internal market for all types of products. This proposal is a first step in the regulation of the rapidly evolving industry of human cells and tissues.

Through registration and listing, EMEA will be able to identify industry participants and the scope of the ATMP produced. This will enable the Agency to monitor the industry more efficiently, distribute new information such as guidance, policies, or requirements, and identify entities that may be subject to EMEA oversight.

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[16] Definitions laid down in Article 3.1 of Directive 2001/83/EC:
This Directive shall not apply to:
1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).

[17] Definitions laid down in Article 3.2 of Directive 2001/83/EC:
This Directive shall not apply to:
2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the official formula).

[18] Possible amendment for to introduce, as addition, in the Whereas (5)

1.6. Definitions

It should be underlined that advanced therapy products covered, are medicinal products, classified in three groups:

–Gene therapy medicinal products, defined Annex I to Directive 2001/83/EC; or

–Somatic cell therapy medicinal products, defined Annex I to Directive 2001/83/CE; or

–Tissue engineered products (TEPs), defined in the proposal.

It is also important to note that the three groups have a common base, which is that of being biological medicinal products, and which therefore require specific control.

1.6.1. The incorporation of the definitions into the text.

Although two of these groups are already defined in previous Directives, *legislative transparency would advise the incorporation of the definitions into the text of the Regulation*, even though making reference to the original Directives. When establishing these definitions it would also be useful to have available those put in force by the United States FDA[19]. It must also be ensured that certain products, despite their complex nature, are adequately defined.

1.6.2 Define the borderline situations

More attention shall be given to define the criteria for determining product classification, in particular, between Tissue Engineered Products, combined ATMPs and medical devices.

It results from the definitions that a combination product, where its cellular or tissue part has only an auxiliary function, is not an ATMP. Thus some combination products will not be regulated at EU-level, especially if the cellular or tissue part is viable or includes engineered cells or tissues. These combination products could be added to the scope of the medical device directive by analogy to medical devices incorporating blood or blood derivatives.

Other medical devices use non-viable animal tissues. For reasons of coherence similar products such as (rendered) non-viable human tissues could be covered by the Medical Device Directive (Dir. 93/42/EC under revision), provided an equivalent level of safety & efficiency requirements are guaranteed, and should then be excluded from the ATMP-proposal.

Furthermore the tissue-engineered products covered by the proposal shall comply with the definition of medicinal products. Therefore tissue-engineered products, not corresponding to that definition, are excluded from the ATMP proposal as well as, actually, from the medical device directives. It is however essential that all kinds of products including tissue-engineered substances, medicinal and other, be subject to an appropriate EU-legislation.

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[19] In the United States, the Food and Drug Administration (FDA) defined human tissue as: Human cells, tissues, or cellular or tissue-based products (HCT/P's) means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/P's include, but are not limited to, bone, ligament, skin, cornea, hematopoietic stem cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue. *Code of Federal Regulations. Title 21, Volume 8.Revised as of April 1, 2005. From the U.S. Government Printing Office* via GPO Access.[CITE: 21CFR1271.3].Pp 716-719.
http://www.fda.gov/cber/tissue/docs.htm
http://a257.g.akamaitech.net/7/257/2422/01apr20051500/edocket.access.gpo.gov/cfr_2005/aprqtr/21cfr1271.3.htm

1.6.3. Establish an arbitration procedure

The proposal states the Regulation does not regulate products that do not qualify as advanced therapy medicinal products, even if based on or consisting of tissues and cells. This warning means that what is understood by advanced therapy products or included in those groups has to be defined in great detail. Given the complexity of the subject the proposal opts for giving the Agency in consultation with the Commission, discretional power to advice on what is and what is not an advanced therapy product. Thus a detailed guideline on this advice procedure defining the data to be provided by the applicant shall be published by the Agency.

But this does not solve the difficulties of interpretation, so that *it would be very convenient to establish an arbitration procedure, regulated by the Agency's Administration Board, to settle disagreements and so provide greater legal certainty*[20].

2. MARKETING AUTHORISATION REQUIREMENTS

2.1. General principles

The principle of compulsory Community authorization for the marketing of gene and cell therapy derived from biotechnology are already established[21]. What is now proposed is to apply the same principle of compulsory Community authorization of 'centralized' marketing to all advanced therapy medicinal products, including those for tissue engineered products, to guarantee the effective functioning of the internal market.
But the proposal takes a step further by intending to create a new specialized Committee within the framework of EMEA to be called a Committee for Advanced Therapies (CAT)

2.2. Technical requirements

Medicinal products derived from tissue engineering will be adapted to the special demands of viability or cell proliferation, the clinical circumstances where the products are used, or to their particular mode of action.

In respect of gene and cell therapy, the type and amount of quality-related, pre-clinical and clinical data necessary to demonstrate their quality, safety and efficacy of the products are already laid down in Annex I of Directive 2001/83/EC and the EMEA guidelines. The same approach is proposed for tissue engineered products, i.e. the Commission is required to complete Annex I of Directive 2001/83/EC in order to establish technical requirements that are specific to these products, and those requirements will be complemented with guidelines, drawn up in consultation with all interested parties.

2.3. Other Requisites

2.3.1. Furthermore the provisions rendered mandatory for clinical trials and post marketing vigilance of products are those applied for generic medical products. Many of these provisions are not applicable for human tissue engineered products and need major modifications, which shall be identified by this Regulation and adopted by the Commission.

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[20] Possible amendment for to introduce in article 18.1 (Addition):
"A detailed guideline on this advice procedure defining the data to be provided by the applicant shall be published by the Agency. The Agency would establish an arbitration procedure, regulated by the Agency's Administration Board, to settle disagreements.

[21] See Annex to Regulation (EC) nº 726/2004.

2.3.2. Directive 2004/23/EC lays down standards of quality and safety for human tissues and cells. As for human tissues and cells contained in advanced therapy medicinal products, Directive 2004/23/EC should apply only as far as donation, procurement and testing are concerned, since the further aspects are regulated by the proposed Regulation.

2.3.3. Advanced therapy medicinal products may also include, as an integral part of the product, medical devices or active implantable medical devices, as defined in Directive 93/42/EEC and in Directive 90/385/EEC respectively. In that case, the 'devise' part shall meet the essential requirements laid down in those Directives.

The EMEA, through the CAT, would provide a 'one-stop shop' system, by evaluating all aspects (including 'devise' aspects) of the product. However, if the devise part has already been evaluated and certified by a notified body, this should be fully taken into account by the CAT for the final evaluation of the product in question.

3. MARKETING AUTHORISATION PROCEDURE

3.1. General Principles

As mentioned above, biological medicinal products for advanced therapy are derived from biotechnology, so that they should be subject to the same fundamental regulatory principles as other types of biotechnology-derived medicines, such as those developed by means of recombinant DNA.

In order to take into account scientific and technical developments, the Commission should be empowered to adopt any necessary changes regarding the technical requirements for advanced therapy medicinal products, in particular for tissue-engineered products.

This is the case for manufacturing- and marketing-authorisation procedures by the Committee for Medicinal Products for Human use (CHMP).

3.1.1. With respect to the manufacturing authorisation, the proposal imposes the application of Directive 2003/94 on Good Manufacturing Practice for Medicinal Products, which is appropriate for gene and cell therapy products. This approach is not appropriate for many tissue-engineered products, which are produced in small quantities and for which the design aspect is predominant.

In fact, tissue engineering is mainly technology oriented, and therefore it is appropriate to evaluate companies on their design capabilities and on the efficiency of their production processes control.

An appropriate solution would be to recognize the equivalence between a GMP based manufacturing license and a manufacturing authorisation on the basis of an appropriately implemented Quality Management system ensuring product conformity and the application of a product follow-up and vigilance system in accordance with the appropriate dispositions for the finished products.

The full Quality Assurance system certification approach specified in the Medical Device directive 93/42/EC Annex II, adapted for tissue engineered products and taking into account ISO 9001:2000, would be appropriate for a Quality Management based manufacturing authorisation.

The proposal should be amended to allow either a GMP or a QA approach.

3.1.2. Considering the importance of design aspects and technologies involved for TEPs and the absence of Mutual Recognition Agreements, *the marketing authorisation procedures actually foreseen and based upon pharmaceutical legislation for products manufactured in third countries should be reviewed and modified appropriately to ensure a plain level field.*

4. SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Specific rules are laid down, adapting the requirements in Directive 2001/83/EC as regards the summary of product characteristics, labeling and package leaflet to the technical specifics of advanced therapy medicinal products.

The product specifications with respect to labeling and packaging are modified by the ATMP proposal (Cfr. Annexes II to IV) to take into account the characteristics of advanced therapy products but should be better specified in particular for TEPs.

Some sectors argue that the package leaflet is not necessary in this area. However, their arguments are inconsistent and it is not acceptable to deprive the patients of necessary information. It must be remembered here that the basic sense of the EU legislation is to consider the document "Summary of Product Characteristics" (SPC) and the Package leaflet as the only source of official, scientific and independent information for every type of medicinal product. The SPC is directed at health professionals and the Package leaflet to the patients. This must not be forgotten.

5. POST-AUTHORISATION REQUIREMENTS

5.1. Post-authorisation issues

By their very nature, advanced therapy medicinal products require that the appropriate risk management system be put in place to address these critical questions. The proposal puts forward the novel aspect of possibly demanding as part of the marketing authorization that the applicant establishes a risk management scheme to detect, prevent or minimize the risks inherent in advanced therapy medicinal products.

Likewise a system allowing complete traceability of the patient, the product and its starting materials, is essential to monitor the safety of advanced therapy medicinal products in a long-term perspective, and is therefore required. This traceability system shall be compatible with the requirements laid down in Directive 2004/23/EC as regards the donation, procurement and testing of human tissues and cells, including the aspects related to data protection, confidentiality anonymity of both donor and recipient.

Long-term follow-up of patients and pharmacovigilance are crucial aspects of advanced therapy medicinal products. A system that permits the complete traceability of the patient, the product and of its starting materials and safety must be established that guarantees its consistency and compatibility with the requirements for traceability laid down in other Directives[22]

[22] See Directive 2004/23/EC on human tissues and cells, and in Directive 2002/98/EC on human blood and its component that modifies Directive 2001/83/EC (DO L 33 of 8.2.2003, p. 30.). The system of traceability must likewise respect the provisions of Directive 95/46/EC relating to protection of physical persons as far as the treatment of personal data and the free movement of these data are concerned (DO L 281 of 23.11.1995, p. 31. Directive modified by Regulation (EC) n° 1882/2003 (DO L 284 of 31.10.2003, p. 1).

The manufacturer shall set up the appropriate systems to ensure product follow-up and to collect and analyze the product adverse effects, which the medical profession informs him of.
The Member States and the EMEA shall participate in the operation of the overall system of product surveillance. The provisions of Regulation 726/2004 title II Ch. 3.are a good basis for specific ATMP dispositions.

5.2 The Challenge of Traceability

Traceability is an essential issue for this type of product and the proposal stresses the need to establish a traceability system. The problem is that the process of donation, processing, storage and application of tissues and cells involves different institutions: Tissue Banks, which have data on donations; manufacturers (applicants); hospitals, which make the clinical application of these products. And cooperation among all these partners is crucial to ensure traceability and the maintenance of a high level of health protection. The actual wording on traceability is not clear enough.

Article 16 of the proposal for the Regulation describes, very precisely, the objective to be achieved, but says nothing of the means to do so. It not consistent to establish aims, yet not establish the means. The only real possibility of effectively carrying out traceability is by establishing a general requirement, through a computer procedure that can be implemented from the taking of the starting materials until their application to a specific patient. But for this, other decisions are needed that the Commission is still in no position to take. An obligation is needed that every medicinal product must be assigned a European authorisation and identification. Moreover, a harmonised bar code must be introduced at the European level.

It is not enough to demand that the holder of a marketing authorisation for an advanced therapy medicinal product shall establish and maintain a system ensuring the traceability of each product. Nor is it enough to state that the treatment institutions shall establish and maintain a system for patient and product traceability. The requirements must be laid down, but the methods to achieve them are needed too. It's surprising that the EU has still not established a global compatible harmonised computer system. Much money is being spent on partial solutions that do not take into account the common challenge. Each citizen must have a global, personal health card that contains her/his clinical history and administrative data of identification and social security system. This personal information set out on the health card should be readable by the terminals of doctors and hospitals throughout the EU, giving access to hospital databases, while respecting the Directives on personal and health data. All this is technically possible. But funds of the EU, national and regional authorities are being wasted in projects that are not harmonised. It is of the greatest urgency that common aims and the harmonised means to put them into effect are established.

5.3. The Need to Impose Bar Code Label Requirements or latest relevant technologies in the EU

To achieve these objectives with the efficacy required it is necessary to introduce into the Proposal a requirement for Bar Code Label Requirements or latest relevant technologies (RFID, Radio Frequency Identification)for Advanced Therapies in the EU[23]. This could be initiated, precisely, with advanced therapy medicinal products, and subsequently extended to other medicinal and health products. A period of two years for the implementation of the system could be allowed. It would not have to be complicated, since there is experience, such a system having already been introduced by the FDA in the United States. In an effort to improve patient safety in the hospital setting by reducing medication errors, the Food and Drug Administration (FDA) published in 2004 a final rule titled, Bar Code Label Requirements for Human Drug Products and Biological Products[24].

6. INCENTIVES

There are problems connected with securing intellectual property protection in tissue engineering. It is difficult to describe cells in detail: what has been invented is a process not a product, and protecting a process is not always possible in patent legislation. Lack of protection for IPR and fears about product liability if there are adverse results may hold back innovation in tissue engineering. The products would be better protected by the data exclusivity that medicines enjoy.

Specific support measures might be considered to ensure product development and market authorisation is not excessively burdensome for small manufacturers. Advanced therapy medicinal products continue to be emerging technologies requiring much investment and support. Its market is still very limited and its risks high. Therefore, the EU must bring in the right incentives, which should be complemented by national incentives.

The incentives at Community level set out in the Proposal for the Regulation are appropriate.

6.1. Competitiveness aspects

A study performed by the European Commission in the year 2003 indicates that in Europe 113 tissue-engineering companies have been identified

The commercial tissue-engineering sector in Europe is characterised by small research-biotechnology companies. The markets for ATMP appear localised and fragmented. However, there is as yet no instance of a product that is available in all EU member states. Access to markets, however, also depends on other factors, such as awareness among doctors and patients, and also reimbursement mechanisms.

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[23] Possible amendment for to introduce in the Article 16 (7):
The Commission shall introduce a requirement for Bar Code Label or latest relevant technologies (RFID, Radio Frequency Identification)for Advanced Therapies in the EU.

[24] "Bar Code Label Requirements for Human Drug Products and Biological Products;
Final Rule". *Federal Register* / Vol. 69, No. 38 / Thursday, February 26, 2004 / Rules and Regulations
http://www.fda.gov/cber/rules/barcodelabel.pdf

By subjecting TEPs to stringent scientific assessment the regulation could increase patients' trust and so lead to more rapid growth of the market as a whole. This might improve the position of SMEs by making it easier for them to obtain finance. The impact of the tissue-engineering sector on employment in the EU is currently slight. Tissue engineering is a sector requiring highly qualified staff to work in research and development, production, the regulatory authorities and hospitals. Companies from outside the EU might be attracted by the large single market .If the regulation built trust in this new technology, it would encourage its acceptance in medical practice and reimbursement policies[25]

6.2. Assessment

The main cost in implementing this rule is staff time. This rule is the first step in creating a tiered, risk-based regulatory scheme that will tailor the degree of scrutiny afforded to different ATMPs to the risks associated with each of them. Through registration EMEA will acquire the information needed to characterize the nature and extent of ATMP. This information will enable EMEA efficiently and effectively to respond to emerging public health concerns related to human cells or tissue.

To alleviate the impact on entities, especially small entities, EMEA will facilitate the use of electronic submissions and electronic signatures.

The environmental risks of producing and using ATMPs are generally considered to be low. Moreover, if future ATMP include genetically modified cells, the legislation on genetically modified organisms is applicable.

7. Committee for Advanced Therapies (CAT)

Given the specificity of the medicinal products called advanced therapy medicinal products, it was decided that a special committee within EMEA should be created, a Committee for Advanced Therapies (CAT), which the present Committee for Medicinal Products for Human Use (CHMP) will consult on the assessment of data concerning advanced therapy medicinal products while still maintaining responsibility for the final scientific opinions issued. This is the most significant modification of the new Proposal. The CAT will work in close collaboration and under the general supervision of the CHMP.

A clearly defined procedure is laid down with strict deadlines to avoid any delays in the marketing authorisation of these products. The composition of this new Committee will reflect the multidisciplinary character of the field and ensure adequate coverage of the scientific areas relevant to advanced therapies.

7.1. Some Observations on the Composition and Functions of the Committee for Advanced Therapies (Article 21)

The proposal to create a special Committee for Advanced Therapies, working in close collaboration with the CHMP, responding to the concern of scientific, doctors, professionals, industrialists and lawyers, shows the growing tendency of the European Commission to multiply the number of Assessment Committees, raising the fear of a loss of unity and criteria when evaluating medicinal products in the EU.

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[25] http://lifesciences.jrc.es/docs/TE_WP4_FinalReport.pdf

It may be that the formula proposed combines necessary specialization with the necessary unity of criteria. If that essential criterion is established, there are a multitude of possibilities to appoint the most appropriate and efficient Committee. Certainly, Parliament and perhaps the Council will have different opinions with respect to the Commission's proposal. Here one can only suggest some possible change, knowing full well that other options may exist, depending on where the political, legal and technical emphasis is put. The main legal values at stake are the uniqueness of criteria, scientific rigour, and the global legitimacy of the EU. As the responsible for the assessment Report and the opinion is EMEA/CHMP, the participation of all Member States in the decision-taking procedures is guaranteed, unity of criteria is assured and possible objections may be settled and approved for ethical reasons to accept within the Community procedures, the non-application of marketing authorisation of any advanced therapy medicinal product in the State or States that has asserted the ethical objection, as foreseen in the draft Regulation.

The specialised scientific character of the CAT would be strengthened by exempting it from the requirement that all Member States are represented. At the same time, it would gain in efficacy and flexibility if there were no limitation that the Rapporteur or Co-Rapporteur, has necessarily to be a member of the CHMP.

The existence of a balanced CAT, with experts and, members of the Committee for Medicinal Products for Human Use, who are people with experience of managing centralized procedures within the context of a regulatory process, will be essential. This will ensure the high quality of scientific expertise on the CAT based in their specific product knowledge rather then based upon nationality. People will be nominated solely based on expertise. The composition of the CAT should indeed reflect the nature of this emerging field and ensure coverage of scientific areas relevant to TEPs, somatic cell therapy products and gene therapy products.

The CAT should be given the authority to elaborate a draft opinion on marketing authorisation, which should, in principle, be the basis for the opinion of the CHMP. There is no need to call on specialists in the field of ethics, since these problems, by the express decision of the European legislation, have remained within the competence of the Member States and there is no room for any type of ethical debate in the evaluation of medicinal products within the Committees.

8. GENERAL AND FINAL PROVISIONS

The final articles of the Proposal are devoted to specifying the legal instrument that is going to be used, preferably, to adopt the technical Directives of Adaptation of Annexes, which will be done in accordance with Council Decision 1999/468/EC laying down the procedures for the exercise of implementing powers conferred on the Commission. The amendments to introduce into the base Regulation (Regulation (EC) No 726/2004) and Amendments to Directive 2001/83/EC are incorporated in the proposal as well as questions of interest for the Transitional Period.

9. Comments on the legislative approach

9.1. The actual proposal establishes three levels of dispositions:

1. Specifications, adopted by the Council and Parliament, being the essential elements of the legislation;
2. Product specific amendments and complements to applicable measures to be adopted by the Commission;
3. Guidelines established either by the Commission or by the Agency.

The use of a hierarchy of procedures seems sensible. This intention needs to be followed through by making the detailed technical requirements specific and appropriate to the nature of the products and the procedures.

9.2. From the comments made in previous paragraphs it appears that, in particular for TEPs, many and often major amendments are necessary. The work to be performed is complex and not free from difficulties. For this reason and to allow parliamentary control it would be appropriate that the mandate, given to the Commission, be spelled out by the actual ATMP proposal and not be left completely open ended.

9.3. The amendments and complementary specifications will be taken in accordance with Decision 1999/468/EC of the Council of 28 June 1999, which established the procedure or the exercise for the enforcement competences attributed to the Commission[26].

These competences are delegated by the ATMP Regulation, which thus must be adopted before the Commission can adopt the necessary amending measures. This creates a situation whereby important specifications for TEPs will be adopted at a later date then the adoption date of the ATMP-proposal. In order to ensure legal certainly, it shall be ensured that the application date of the ATMP Regulation and of the relevant amending measures are the same.

9.4. The above points reinforce the need for codifying the whole sector of the legislation applicable to Advanced Therapy Medicinal Products in the near future.

[26] DO L 184 of 17.7.1999 p. 23

10. Ethical Aspects

The proposed Regulation respects fundamental human rights and observes the principles reflected in the Charter of Fundamental Rights of the European Union[27]. It also takes into account the Convention for the protection of human rights and dignity of the human being with regard to application of biology and medicine[28]. Furthermore, it echoes Directive 2004/23/EC, which mentions in the Preamble, that human tissue- and cell- based products should be founded on the philosophy of voluntary and unpaid donation.

There is wide variety of national regulatory regimes for research on early embryos and several member states have no legislation to govern Embryonic Stem cell research. An additional protocol was adopted in 2002[29], but this reference to the Convention of the Council of Europe is not consistent with the legislation and seems little more than rhetoric, in part because the text itself is not determinant.

There are certain ambiguities in the Council of Europe Convention on Human Rights and Biomedicine regarding the creation and use of human embryos for experimental or therapeutic purposes and the situation is made worse by the failure of the majority of the Member States to ratify it. It cannot be thought that the mere mention of the Council of Europe Convention on Biomedicine will make its contents obligatory on all the EU members, and even more when many have, expressly, not ratified it. It is hard to understand the proposal's lack of legal strictness and poor draftsmanship.

10.1. Need to Define the Procedure for Application of the "Objection on Ethical Grounds Clause".

The possible use of embryonic cytoblasts does not enjoy majority consensus in the EU, so that in the Directive on human cells and tissues (Directive 2004/23/EC), it was decided that the regulation of such use or prohibition must remain a national responsibility[30]. To clarify this question explicit provisions have been introduced in the proposal. The Member States shall communicate the national legislation concerned to the Commission and must give notice of the technologies that will be prohibited.

The proposal for the Regulation accepts the possibility that any Member State, for ethical reasons, does not accept marketing authorisation granted by the Agency, but this should not mean that after centralised authorisation has been obtained any complementary application need be made to the national authorities. This would be a violation of centralised authorisation procedure on the part of the EMEA, with serious institutional consequences and the origin of all types of disagreements.

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[27] DO C 364 of 18.12.2000, p. 1.

[28] Convention on human rights and biomedicine, Oviedo, 4 April 1997.
http://conventions.coe.int/treaty/en/treaties/html/164.htm.

[29] Council of Europe, *Additional Protocol to the Convention on Human Rights and Biomedicine, on Transplantation of Organs and Tissues of Human Origin.* 2002: Strasbourg.
available at http://conventions.coe.int/treaty/EN/Treaties/Html/186.htm

[30] Recital 12 and Article 4 (3), of Directive 2004/23/EC.

To avoid this, the draft should contain clauses that state clearly, "during the assessment process of an advanced therapy medicinal product any Member State, through its representatives on the CHMP or CAT can put forward "an objection on ethical grounds", based on national legislation in force, not to accept the marketing of such medicinal product within its territory. If approved, this exception will be set out in the Assessment Report that EMEA remits to the Commission. In turn, the Commission will include this exception in its final scientific Report granting authorisation. The debate on this objection will be held and will conform to the assessment procedure in a similar manner to the other scientific and technical objections"[31].

Thus, is necessary an amendment to the CHMP opinion procedure where member states may request to be withdrawn from the voting pool should a vote be required. Committee members cannot object to the approval solely based on local legal arguments.

For all this complexities it is necessary ask is will be better to introduce for these products rather the Mutual Recognition Procedure than an problematical construct to keep the centralized procedure.

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[31] Possible amendment for to introduce in the Article 9 (6)