9.2 Content of a "Request for VHP"

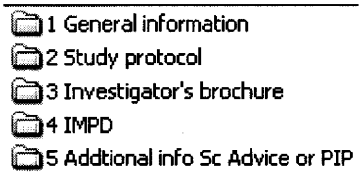
The following information should be contained in a request for VHP:

1. Covering letter including the EudraCT number and a short description of the key features of the CT

2. List of the NCAs the applicant intends to submit a CTA in the national phase
3. core CTA EudraCT form, (common information for all MS)
4. Protocol related folder with study protocol including synopsis
5. Investigator's brochure

6. IMP dossier, as defined in EudraLex - Volume 10 (including viral safety and IMPD on the Placebo, if applicable)
7. IMP additional information (if not included in IMPD): manufacturing authorisation; GMP compliance certificate; importation authorisation; certificate of analysis, if applicable; authorisation for special characteristics of products e.g. GMO or radioelements.
8. NIMPs Dossier according to ANNEX I, if applicable
9. Copy/summary of any scientific advice from any competent authority or EMEA and PIP summary, if applicable

For FIH MN-CTs, all applicable clinical and non-clinical aspects specific to the product under investigation and their potential impact on the study design and/or on the conduct of the clinical trial should be discussed, as outlined in the Guideline on strategies to identify and mitigate risks for FIH-CTs with IMP (EMEA/CHMP/SWP/294648/2007), or justification should be provided as to why the points have not to be addressed in the CT documentation.
Electronic structure of the VHP application:



10 ANNEX I

10.1 HARMONISED REQUIREMENTS FOR NON INVESTIGATIONAL MEDICINAL PRODUCTS IN CTA SUBMISSIONS

Within the design of a clinical trial, there may be the use of components other than Investigational Medicinal Products (IMPs). Examples of such other products are rescue medication, challenge agents and background therapy. Such products are referred to as non-investigational medicinal products – NIMPs. The definition of a NIMP is provided in Chapter III of Volume 10 of The Rules Governing Medicinal Products in the EU (Guidance on Investigational medicinal products (IMPs) and other medicinal products used in Clinical Trials).

The status of such products has been addressed in Annex 13 of Volume 4 of The Rules Governing Medicinal Products in the EU and in Commission guidance (Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial).

The safeguarding of the clinical trial subject, in accordance with Article 3 of Directive 2001/20/EC and the objectives of this Directive in general, is ensured *inter alia* by guaranteeing the quality and safety of the products and substances used in the trial. As NIMPs do not fall within the definition of investigational medicinal products, Articles 13 and 14 of Directive 2001/20/EC are not directly applicable. To meet the requirements of Article 3(2) of Directive 2001/20/EC, and as referred to in Article 6(3) relating to the protection of the trial subject, the same level of quality and safety should be ensured for the NIMPs as for the IMPs used in the trials. Information on the ways in which sponsors can ensure the quality of the NIMP in terms of the appropriateness of the manufacturing site is included in Annex 1.

The Commission guidance strongly recommends that, where possible, non-investigational medicinal products (NIMPs) have a marketing authorisation in the Member State where the trial is being conducted. Where this is not possible, the next choice would be a product which has a marketing authorisation in an other EU Member State. On a case-by-case basis, it may be possible for sponsors to justify the use of NIMPs obtained from an ICH region [USA. Japan] or from a Mutual Recognition Agreement-partner country [Australia, Canada, New Zealand, Switzerland]. A Mutual Recognition Agreement provides assurance that equivalent GMP standards are applied by both parties of the agreement. In line with the approach in the *Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials* - CHMP/QWP/185401/2004, the data requirements to support the use of products from these countries are reduced.

The sponsor should provide details of the NIMPs and their proposed use in the trial protocol. Information on the NIMP should be provided in accordance with the guidance provided below. To facilitate the preparation of a harmonised dossier, documents submitted to the Competent Authority may be submitted in English.

The sponsor is responsible for implementing a system to ensure that the trial is conducted and data are generated in accordance with the principles of Good Clinical Prac-

tice. To comply with these principles, a trial has to be conducted according to the protocol and all clinical trial information should be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified. In this context, the sponsor should implement a system allowing traceability of medicinal products which allows adequate reconstruction of NIMP movements and administration, taking into account the purpose of the trial and trial subjects' safety. It has at least to include a procedure, established with the investigator and if applicable, with the hospital pharmacy, to record which patients received which NIMPs during the trial with an evaluation of the compliance.

1. BACKGROUND THERAPY/RESCUE MEDICATION

Background therapy

This type of medicinal product is administered to each of the clinical trial subjects, regardless of randomisation group, to treat the indication which is the object of the study. Background treatment is generally considered to be the current standard care for the particular indication in the Member State concerned. In these trials, the IMP is given in addition to the background treatment and safety/efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared to an active comparator or to placebo plus background treatment. Sponsors should note that the Commission guidance strongly recommends that, where possible, non-investigational medicinal products (NIMPs) have a marketing authorisation in the Member State where the trial is being conducted. Where this is not possible, the next choice would be a product which has a marketing authorisation in an other EU Member State. In situations where the background therapy does not have a marketing authorisation in the Member State where the trial is being conduction, a justification for its use should be provided.

Rescue medication

Rescue medications are medicines identified in the protocol as those that may be administered to the patients when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation.

The following examples lay out the contents of the NIMP dossier where the NIMPs are used as background therapy or rescue medication.

1.1 NIMP is a marketed medicinal product in the concerned Member State

Simplified dossier is required containing

- copy of the SmPC
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial

1.2 NIMP is a marketed medicinal product in an other EU Member State

Simplified dossier is required containing

- copy of the SmPC (translated as necessary)

- information on any repackaging and/or relabelling and a list of sites involved
- acceptable evidence of GMP compliance [manufacturer's authorisation/QP certification for non-EU sites] for the repackaging and/or relabelling or a justification for its absence
- justification of the use of the product if there is a comparable product authorised in the concerned Member State but one with a marketing authorisation in an other EU Member State is used in the trial
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial

1.3 a NIMP is a marketed medicinal product in an ICH country or a country which has Mutual Recognition Agreement (MRA) with the EU

Simplified dossier is required containing

- evidence of its regulatory status in the country of origin
- copy of the SmPC or local equivalent (translated as necessary)
- information on any repackaging and/or relabelling and a list of sites involved
- acceptable evidence of GMP compliance [manufacturer's authorisation /QP certification for non-EU sites]for the repackaging and/or relabelling or a justification for its absence
- importer's authorisation
- justification for the use of the product if there is a comparable product authorised in the concerned Member State or an other EU Member State but one with a marketing authorisation an ICH /MRA country is used in the trial
- justification for the use of the product if there is no comparable product licensed in the concerned Member State or it is used outside of its marketing authorisation in the ICH/MRA country
- justification for the safe and effective use of the product in the trial, including any potential for interactions between the NIMP and the IMPs to be used in the trial,
- confirmation of reduced testing (e.g. identity) by analytical testing or an alternative appropriate method

1.4 NIMP is a marketed medicinal product in a third country (not ICH or MRA country)

Full dossier is required containing

- documents on quality and manufacturing as per the *Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials* - CHMP/QWP/185401/2004
- results from non-clinical and clinical studies
- acceptable evidence of GMP compliance including the site of batch release by a Qualified Person (QP)
- manufacturer's authorisation/importer's authorisation
- justification for the safe and effective use of the product in the trial taking into account any potential for interactions between the NIMP and the IMPs to be used in the trial and if it is used outside of its marketing authorisation

- justification of the use of the product if there is a comparable product authorised in the concerned Member State but one with a marketing authorisation in a third country is used in the trial

1.5 NIMP has no marketing authorisation (is manufactured specially for use in the proposed trial) but the drug substance is contained in a medicinal product marketed in the concerned Member State or an other EU Member State

Full dossier is required containing

- documents on quality and manufacturing as per the *Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials* - CHMP/QWP/185401/2004
- acceptable evidence of GMP compliance including site of batch release by QP
- manufacturer's authorisation/importer's authorisation
- justification for the safe and effective use of the product in the trial

1.6 NIMP is defined in the protocol but is not fixed to a particular product

In this situation, the product(s) to be used is/are authorised in the Member State in which the trial is being undertaken but a particular brand is not specified in the protocol.

This information should be included confirmed in the covering letter. No additional information is required.

2. CHALLENGE AGENTS/ MEDICINAL PRODUCTS USED TO ASSESS END-POINTS

Challenge agents

Challenge agents are usually given to trial subjects to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed. They may be substances without a marketing authorisation, however some have a long tradition of clinical use.

Medicinal products used to assess end-points

This type of NIMP is given to the subject as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.

The following examples lay out the contents of the NIMP dossier where the NIMPs are used as challenge agents or as medicinal products used to assess end-points.

2.1 NIMP is a marketed medicinal product in the concerned Member State

Simplified dossier is required containing

- copy of the SmPC
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial

2.2 NIMP is a marketed medicinal product in an other EU Member State, in an ICH country or in a country which has a Mutual Recognition Agreement with the EU

Simplified dossier is required containing

- evidence of its regulatory status in the country of origin
- copy of the SmPC [or equivalent document] translated as necessary
- information on any repackaging and list of sites involved
- acceptable evidence of GMP compliance for the modification (including repackaging) - manufacturer's authorisation/QP certification (for non-EU sites) or justification for its absence
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial
- reduced testing (e.g. identity) by analytical testing or an alternative appropriate method
- importer's authorisation for ICH/MRA marketing authorisations
- justification of the use of the product if there is a comparable product authorised in the concerned Member State but one with a marketing authorisation in an other EU Member State, ICH country or MRA country is used in the trial

2.3 NIMP is a marketed medicinal product in an other EU Member State, in an ICH country or in a country which has a Mutual Recognition Agreement with the EU but has been modified for use in the trial

Simplified dossier is required containing

- evidence of its regulatory status in the country of origin
- copy of the SmPC [or equivalent document] translated as necessary
- information (as per chapter 4 of the *Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials* - CHMP/QWP/185401/2004) on any modification to the product and list of sites involved
- acceptable evidence of GMP compliance for the modification - manufacturer's authorisation/QP certification (for non-EU sites) or justification for its absence
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial
- reduced testing (e.g. identity) by analytical testing or an alternative appropriate method
- importer's authorisation for ICH/MRA marketing authorisations
- justification of the use of the product if there is a comparable product authorised in the concerned Member State but one with a marketing authorisation in an other EU Member State, ICH country or MRA country is used in the trial

2.4 NIMP is an unlicensed product previously authorised for use as a NIMP in a trial conducted in the concerned Member State by the same sponsor or where a letter of access to the data from the sponsor of the previous trial is available

Simplified dossier is required containing

- EudraCT number of previous trial
- confirmation that the trial population is in line with that of the previously approved trial or justification of any differences
- confirmation that the dose/duration of dosing does not exceed that of the previously approved trial or justification of any differences
- justification for the safe use of the product in the trial including any potential for interactions between the NIMP and the IMPs to be used in the trial
- confirmation that there were no safety or quality issues arising from the use of this product in the previous trial
- confirmation that the product is manufactured and controlled (including formulation, site of manufacture, quality control and specifications) in line with the conditions of the previously approved trial taking account of both the initial NIMP dossier and any subsequent amendments

2.5 NIMP is an unlicensed product which has been used as an IMP in a previous trial conducted in the concerned Member State by the same sponsor or another sponsor where a letter of access to the data from this sponsor is available

Simplified dossier is required containing

- EudraCT number of previous trial
- confirmation that the trial population is in line with that of the previously approved trial or justification of any differences
- confirmation that the dose/duration of dosing does not exceed that of the previously approved trial or justification of any differences
- justification for the safe use of the product in the trial including any potential for interactions between the NIMP and the IMPs to be used in the trial
- confirmation that there were no safety or quality issues arising from the previous trial
- confirmation that the product is manufactured and controlled (including formulation, site of manufacture, quality control and specifications) in line with the conditions of the previously approved trial taking account of both the initial IMP dossier and any subsequent amendments

2.6 NIMP is an unlicensed product where the active moiety has been previously administered to humans

Simplified dossier is required containing

- rationale for its safe use in the trial including information on the extent of previous human exposure, including any potential for interactions between the NIMP and the IMPs to be used in the trial
- evidence that existing nonclinical safety data support the use in the proposed trial

- information on the composition, method of manufacture and controls applied to the product
- confirmation of the site of manufacture of the product
- confirmation of the appropriateness of the manufacturing site (eg a copy of the manufacturer's authorisation/EU QP declaration/ importer's authorisation)
- confirmation of the mechanism for ensuring the quality of the product (eg QP release)

Annex 1

EVIDENCE OF APPROPRIATENESS OF THE MANUFACTURING SITE AND MECHANISM FOR CONTROLLING QUALITY OF THE PRODUCT

Acceptable evidence of the appropriateness of the manufacturing site and the mechanism for controlling the quality of the product includes, but is not limited to, the following

1. Manufactured under the provisions of a manufacturer's authorisation for the manufacture of marketed products or IMPs and QP released
2. Manufactured under national provisions to the principles of GMP and released for use by an appropriately experienced individual

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods

CONSULTATION PAPER

HUMAN TISSUE ENGINEERING AND BEYOND:

PROPOSAL FOR A COMMUNITY REGULATORY FRAMEWORK ON ADVANCED THERAPIES

04 May 2005

This document does not represent an official position of the European Commission. It is a tool to explore the views of interested parties on a preliminary proposal. The suggestions contained in this document do not prejudge the form and content of any future proposal by the European Commission.

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TABLE OF CONTENTS

1. INTRODUCTION

1.1. The current picture

The advancement of science in the fields of biology, biotechnology and medicine, has fuelled the development of promising gene- and cell-based approaches for the prevention and treatment of diseases or dysfunctions of the human body. A number of **gene therapy and somatic cell therapy** products are already being tested at clinical level for the treatment of various inherited diseases, cancer, diabetes, Parkinson's disease and other neurodegenerative disorders.

In addition, a new biotechnology area has emerged: **human tissue engineering**, which combines various aspects of medicine, cell and molecular biology, materials science and engineering, for the purpose of regenerating, repairing or replacing diseased tissues. Current applications of this nascent field of "regenerative medicine" include treatment for skin, cartilage and bone diseases or injuries. More complex products – such as heart valves, blood vessels or heart muscle tissue – are currently in development, and could reach the Community market in a near future[1].

1.2. Advanced therapies: a coherent ensemble

These three kinds of **advanced therapies** (gene therapy, somatic cell therapy, and human tissue engineering) are expected to have a major impact on public health, by improving the quality of life of patients and changing medical practice significantly. Moreover, they constitute a coherent ensemble insofar as they share several key scientific, economic, and ethical features. For example:

- They are based on complex, highly innovative manufacturing processes aiming at modifying genetic, physiological or structural properties of cells and tissues. The specificity of the product precisely lies *in* the process.

- Regulatory and scientific expertise for the evaluation of advanced therapies is scarce: pooling of that expertise at Community level is therefore essential to ensure a high level of public health protection.

- Traceability from the donor to the patient, long-term patient follow-up and a thorough post-authorisation risk management strategy are crucial aspects to be addressed when evaluating advanced therapies.

- Advanced therapy products are usually developed by innovative small and medium-sized enterprises, highly-specialised divisions of larger operators in the Life Science sector (biotechnology, medical devices and pharmaceuticals), or hospitals. They are subject to rapid and often radical innovation.

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[1] See Bock, A.K., Ibarreta, D., Rodriguez-Cerezo, E.: *'Human tissue-engineered products - Today's markets and future prospects'*, Joint Research Centre - Institute for Prospective Technological Studies (European Commission), EUR 21000 EN, October 2003.

1.3. The current regulatory gap and its implications on public health

Despite these common elements, the regulatory picture for advanced therapies remains incomplete. In particular, while products intended for gene and somatic cell therapy have been classified as medicinal products and regulated as such in the Community[2], tissue-engineered products currently lie outside of any legislative framework (Figure 1). This leads to divergent approaches across Member States as to their legal classification and authorisation, thereby impairing the free movement of human tissue engineered products in the Community, and hindering patients' access to these innovative therapies.

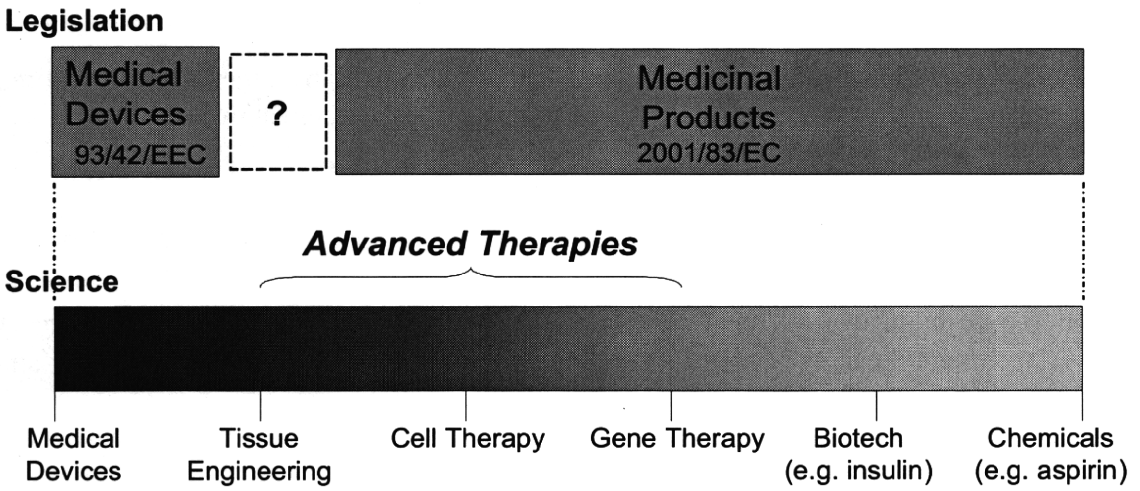

Figure 1: Spectrum of products and corresponding legislation. The main Directive on medical devices is Dir. 93/42/EEC. The main Directive on medicinal products is Dir. 2001/83/EC.

1.4. Previous consultations

In 2002 and 2004, the European Commission (DG Enterprise) launched two public consultations, in order to assess the need for a legislative framework on tissue engineering[3]. These consultations highlighted a broad consensus in favour of a specific, harmonised and coherent EU regulatory framework covering human tissue engineered products, as well as other cell/tissue based products. Stakeholders, in particular the industry, stressed the need to **establish legal certainty** in that emerging field, as rapidly as possible. They also recommended that any new initiative should comprehensively address not only existing, but also future cell/tissue based products. Finally, they provided valuable input on key procedural and technical aspects (notably the scope, definitions, marketing authorisation requirements and borderline issues) that any proposal for a Regulation in this area should address.

1.5. Objectives

On the basis of the outcome of these previous consultations, the Commission (DG Enterprise and Industry) has prepared a proposal to **bridge the regulatory gap**, by addressing all advanced therapies (*i.e.* gene therapy, somatic cell therapy, and human

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[2] Part IV of Annex I to Directive 2001/83/EC, as amended by Directive 2003/63/EC, OJ L159, 27.6.2003, p.46. See also *'Commission Communication on the Community marketing authorisation procedures for medicinal products'*, 98/C 229/03, OJ C 229/4, 22.7.1998.

[3] See http://pharmacos.eudra.org/F2/advtherapies/index.htm

tissue engineering) within **a single, integrated and tailored framework**, fully taking into account their scientific and technical inherent characteristics, as well as the specificities of the economic operators concerned.

More specifically, this approach is intended to fulfil the following key objectives:

- To guarantee a **high level of health protection** for European patients treated with advanced therapies;
- To **harmonise market access** for advanced therapies by establishing a tailored and comprehensive regulatory framework for their authorisation, supervision and post-authorisation vigilance;
- To **foster the competitiveness** of European undertakings operating in this field;
- To **provide overall legal certainty**, while allowing for **sufficient flexibility at technical level**, in order to keep the pace with the evolution of science and technology.

2. PRESENTATION OF THE PROPOSAL

2.1. The Regulatory Strategy

General approach

The proposed approach is based on a single, integrated regulatory framework for all advanced therapies (Figure 2).

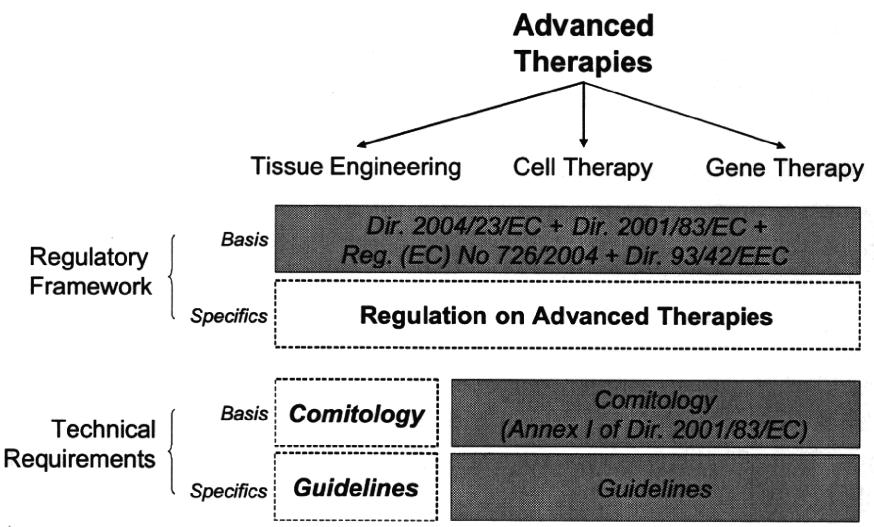

Figure 2: The proposed regulatory strategy. Existing elements are highlighted in orange; elements to be established are highlighted in white, dashed boxes. It is proposed that the main technical requirements are laid down through a 'comitology' procedure. Further technical requirements would be established through guidelines.

The aim of this strategy is to avoid any re-drafting of already-existing and applicable concepts, while focusing exclusively on the key regulatory and technical specificities of the field.

Concretely, the approach is based on 3 levels (Figure 2):

(1) A tailored **Regulation on Advanced Therapies**, covering gene therapy, cell therapy, and human tissue engineered products, which lays down *ad-hoc* regulatory principles for the evaluation and authorisation of these products: marketing authorisation procedure, post-authorisation vigilance, traceability, etc. Such Regulation builds on already-existing legislation, in particular:

- Directive 2004/23/EC, which lays down basic quality/safety requirements on human tissues and cells[4];
- Regulation (EC) No 726/2004, which establishes the so-called 'centralised procedure' and the role/structure of the European Medicines Agency (EMEA)[5];
- Directive 2001/83/EC on medicinal products[6];
- Council Directive 93/42/EEC concerning medical devices[7].

(2) Technical requirements. It is well acknowledged that advanced therapy products are not conventional medicines: therefore, the technical requirements necessary to demonstrate their quality, safety and efficacy (*e.g.* the type of pre-clinical and clinical data required, control of the manufacturing process, etc.) will be highly specific.

As regards gene and somatic cell therapy products, those high-level requirements are already laid down in Annex I to Directive 2001/83/EC[8] (which is amendable *via* a so-called 'comitology' procedure), and further complemented by guidelines[9]. In order to provide for the same level of flexibility, it is proposed to follow a similar approach regarding human tissue engineered products (Figure 2), *i.e.* to lay down the main technical requirements that are specific to these products through a 'comitology' procedure, and to further complement them with guidelines.

(3) Detailed guidelines. As for gene and somatic cell therapy products, it is proposed to establish detailed technical guidance for tissue engineered products through **guidelines**, drawn up either by the EMEA or by the Commission (Figure 2). The fact that expertise is still scarce in this fast-growing, fast-evolving area highlights the importance of extensive and thorough consultation with all interested parties, in particular the industry, for the drafting of these guidelines.

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[4] OJ L102, 7.4.2004, p.48
[5] OJ L136, 30.4.2004, p.1
[6] OJ L311, 28.11.2001, p.67
[7] OJ L169, 12.7.1993, p.1
[8] Annex I to Directive 2001/83/EC, as amended by Directive 2003/63/EC, OJ L159, 27.6.2003, p.46.
[9] See http://www.emea.eu.int/htms/human/itf/itfguide.htm

Legal basis, procedure and choice of legal instrument

The proposal is based on Article 95 of the EC Treaty. Article 95, which prescribes the co-decision procedure described in Article 251, is the legal basis for achieving the aims set out in Article 14 of the Treaty, in particular the free movement of goods, taking as a basis a high level of health protection.

Given the particularities of advanced therapy products, it is essential to provide a robust and comprehensive regulatory framework, which is strictly enforced in all Member States. A Regulation is therefore considered as the most appropriate legal instrument. It should indeed ensure uniform and timely application of the provisions, for the benefit of all actors, including patients, industry and other stakeholders involved in this emerging sector.

2.2. Definitions and Scope

Definitions

Advanced therapy products are defined as medicinal products being either:

- gene therapy medicinal products, as defined in Annex I to Directive 2001/83/EC;
- somatic cell therapy medicinal products, as defined in Annex I to Directive 2001/83/EC;
- human tissue engineered products.

Thus, the proposed definition of advanced therapy builds on already-existing definitions of gene therapy medicinal products and somatic cell therapy medicinal products, which are laid down in Annex I to Directive 2001/83/EC. It also encompasses human tissue engineered products, defined as:

"Any product for autologous or allogeneic use which:

- contains or consists of engineered human cells or tissues; and
- is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue."

"Engineered human cells or tissues" are defined as:

"Cells or tissues removed from a human donor and manipulated *via* a manufacturing process, so that their normal biological characteristics, physiological functions or structural properties are substantially altered."

A human tissue engineered product may incorporate, as an integral part of the product, one or several medical devices within the meaning of Directive 93/42/EEC. It may also contain additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices.

All advanced therapy products, including human tissue engineered products, are considered from a legal viewpoint as medicinal products for at least one of the following reasons:

- They have properties for treating or preventing disease in human beings;

- They are used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action;

- In accordance with the jurisprudence of the European Court of Justice (ECJ) on the matter, they are capable of having a significant effect on the actual functioning of the body[10].

Furthermore, the existence of health risks is traditionally one of the criteria employed by the ECJ for classifying a product as medicinal[11]. It follows from the aim of health protection pursued by the Community pharmaceutical legislation that products presenting potential health risks (as is clear for advanced therapy products) should be covered by the rigorous requirements of that legislation in case of doubt as to their classification.

However, this does not mean that advanced therapy products will be subject to the same technical requirements as 'conventional' medicines. On the contrary, the type and amount of pre-clinical/clinical data necessary to demonstrate their quality, safety and efficacy will be highly specific, fully taking into account their biological, functional and structural characteristics (see Section 2.4).

Scope

The proposal addresses all advanced therapy products falling within the global scope of the Community legislation on medicinal products[12], *i.e. "intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process"*. This should cover, *inter alia*:

- any 'mass production' of advanced therapy products for allogeneic use;

- any advanced therapy product for autologous use which, although being patient-specific by definition, is manufactured in accordance with a standardised, industrial process.

On the other hand, advanced therapy products are sometimes produced on an *ad-hoc*, one-off basis, according to a specific and unique manufacturing process, for the single treatment of an individual patient in accordance with a specific medical prescription. In that case, it may not be appropriate to subject their placing on the market and manufacture to the provisions of this Regulation. They are therefore excluded from the scope of the proposal.

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[10] See cases 227/82, Van Bennekom [1983] ECR 3883 ; C-369/88, Delattre [1991] ECR I-1487 ; C-60/89, Monteil and Samanni [1991] ECR I-1547 ; C-112/89, Upjohn [1991] ECR I-1703 ; C-290/90, Commission v Federal Republic of Germany [1992] ECR I-3317 ; C-219/91, Ter Voort [1992] ECR I-5485.

[11] Monteil and Samanni, paragraph 29; Delattre, paragraph 35; Commission v. Federal Republic of Germany, paragraph 17.

[12] See Article 2(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

Examples:

- A hospital developing an in-house, non-industrial technology based on autologous cells to repair/regenerate cardiovascular tissue for a given patient. Although the resulting product may be considered as an advanced therapy product, it is neither *"prepared industrially"* nor *"manufactured by a method involving an industrial process"*. This case would therefore not be covered by the proposed Regulation, as it falls outside its scope.

- A small and medium-sized biotech company (SME), developing a skin substitute product based on allogeneic cells, produced *via* a standardised, large-scale process. In this case, the product is a tissue engineered product *"intended to be placed on the market in Member States"* and *"prepared industrially"*: it should therefore be covered by the proposed Regulation.

- A large operator, operating at global level, developing a product based on autologous cultured chondrocytes, which are manipulated *via* a well validated and controlled industrial process. In this case, the product is *"manufactured by a method involving an industrial process"*, and should therefore be covered by the proposed Regulation.

In any case, it should be noted that human tissue- or cell-based advanced therapy products lying outside the scope of the proposal will still be subject to the quality and safety standards laid down in Directive 2004/23/EC as regards human tissues and cells.

Xenogeneic tissue engineered products

Tissue engineered products derived exclusively from cells or tissues of animal origin raise highly specific safety and ethical issues. For the moment, it is therefore proposed to exclude them from the scope of the Regulation, with the proviso that this scope be re-assessed at a later stage, to consider their inclusion.

Nonetheless, this Regulation should apply to human tissue engineered products for which tissues and cells of animal origin are used in the manufacture without being present in the final product, or, if present, only in trace amounts and without being viable.

2.3. Marketing Authorisation Procedure

General principles

Experience gained in the area of modern biotechnology, where scientific expertise is often limited, highlights the necessity to establish centralised procedures for the authorisation of biotechnology-derived therapeutic products. This pooling of expertise from all Member States enables to guarantee a high level of scientific evaluation across the European Union, and thus to preserve the confidence of patients and medical practitioners in their evaluation. This is all the more important for advanced therapy products, which often result from highly innovative, not-yet-well-established processes and technologies.

The principle of a compulsory Community marketing authorisation is already established for gene therapy medicinal products and somatic cell therapy medicinal products resulting

from any biotechnology process referred to in the Annex to Regulation (EC) No 726/2004. In this context, it is proposed to apply the same principle of a compulsory, 'centralised' Community marketing authorisation to all advanced therapy products, including human tissue engineered products, in order to ensure the effective operation of the internal market in the biotechnology sector, and to enable undertakings to benefit from direct access to the global Community market. As for other 'centrally-authorised' products, the scientific evaluation would be carried out by Member States experts, at the EMEA.

Committee for Advanced Therapies (CAT)

A committee with expertise in all aspects related to advanced therapy products is central to the proposal and its operation.

Within the EMEA, the Committee for Medicinal Products for Human Use (CHMP) holds the responsibility for drawing up an opinion on any scientific matter concerning the evaluation of medicinal products for human use. Nevertheless, the assessment of advanced therapy products often requires very specific expertise, which goes beyond the traditional pharmaceutical field and covers borderline areas related to other sectors such as biotechnology, medical devices, biochemistry and biophysics. For this reason, it is proposed to create, within the EMEA, a Committee for Advanced Therapies (CAT), to which the CHMP should delegate the assessment of data related to advanced therapy products, whilst retaining responsibility for the final scientific opinions issued (Figure 3).

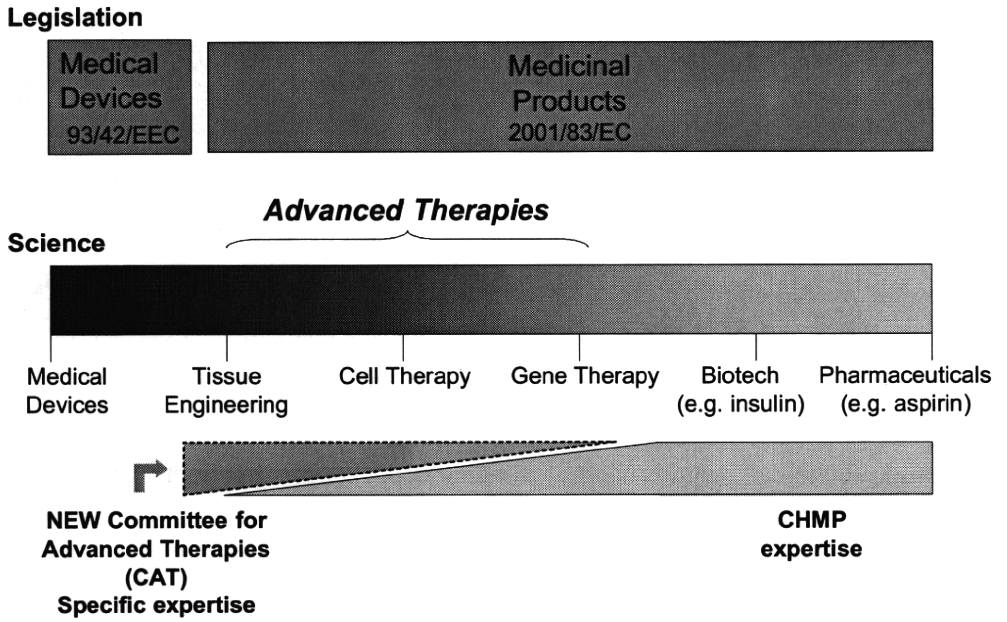

Figure 3: Reinforcing the expertise: the creation of a Committee for Advanced Therapies

The main task of the CAT will be to assess any data related to advanced therapy products. The CAT will work in close cooperation with, and under the general supervision, of the CHMP. A clearly-defined procedure, with strict deadlines, will be established in order to avoid any delays in the marketing authorisation of these products.

The composition of this new Committee will reflect the multidisciplinary nature of the field and ensure appropriate coverage of the scientific areas relevant to advanced therapies, *e.g.* medical devices, tissue-engineering, gene and cell therapy, biotechnology

and tissues/cells-related ethics. Interested parties, such as patient associations, medical practitioners, surgeons or scientists involved in basic research in the field, should also be represented.

In addition, the CAT may also be consulted for other medicinal products which, although not classified as advanced therapy products, may require specific, CAT-related expertise for the evaluation of their quality, safety or efficacy.

Evaluation procedure

As outlined above, the CHMP will delegate the scientific assessment of advanced therapy products to the CAT, in accordance with a specific procedure laid down in the proposed Regulation. A number of mechanisms are foreseen to avoid divergent opinions between the CHMP and the CAT:

- Some members of the CAT are also members of the CHMP;
- Both Committees will share the same rapporteur for the coordination of the evaluation of a given advanced therapy product, thereby preventing any inconsistency;
- If necessary, the Chairman of the CAT will be invited by the CHMP to present the views of the CAT;
- Where the final opinion of the CHMP is not in accordance with the opinion of the CAT, the CHMP will have to explicitly detail the scientific grounds for the differences.

2.4. Marketing Authorisation Requirements

General principles

Broadly speaking, advanced therapy products are biotechnology-derived products. They should therefore be subject to the same overarching regulatory principles as other types of biotechnology-derived medicines, such as products developed by means of recombinant DNA technology or hybridoma and monoclonal antibody methods.

On the other hand, technical requirements for advanced therapy products are clearly highly specific; they differ significantly from those applicable to 'classical' pharmaceuticals, in particular at the clinical level, and evolve rapidly with the advancement of science and technology. Consequently, they must be legally established in a way that provides for sufficient flexibility.

Technical requirements

It is recognised that 'conventional pharmaceutical' technical requirements, as laid down in Module 4/5 of Annex I to Directive 2001/83/EC, are not directly relevant for advanced therapy products, due to their specific structural, functional and biological properties. For example, it may not be possible to perform 'conventional' clinical trials: the clinical development will hence have some special features owing to the complex nature of the products, and will most likely require considerations related to the viability, proliferation, migration and differentiation of cells, to the special clinical circumstances where the products are used, or to their particular mode of action.