XII. REFERENCES

1. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy, March 1998, http://www.fda.gov/cber/gdlns/somgene.pdf.

2. Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products, November 1995, http://www.fda.gov/cder/guidance/phase1.pdf.

3. Final Rule: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, (69 FR 29786, May 25, 2004), http://www.fda.gov/cber/rules/suitdonor.pdf.

4. Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), August 2007, http://www.fda.gov/cber/gdlns/tissdonor.pdf.

5. Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals, July 12, 1993, http://www.fda.gov/cber/gdlns/ptccell.pdf.

6. ICH Guidance on Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products, (63 FR 50244, September 21, 1998), http://www.fda.gov/cber/gdlns/qualbiot.pdf.

7. Guidance for Industry: Source Animal, Product, Preclinical and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans, April 2003, http://www.fda.gov/cber/gdlns/clinxeno.htm.

8. PHS Guideline on Infectious Disease Issues in Xenotransplantation, January 19, 2001, http://www.fda.gov/cber/gdlns/xenophs0101.htm.

9. Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, February 28, 1997, http://www.fda.gov/cber/gdlns/ptc_mab.pdf.

10. Manual of Standard Operating Procedures and Policies: Intercenter Consultative/Collaborative Review Process, Version 4, dated June 18, 2004, http://www.fda.gov/oc/ombudsman/intercentersop.pdf.

11. FDA Guidance Concerning Demonstration of Comparability of Human Biological Product, Including Therapeutic Biotechnology-derived Products, April 1996, http://www.fda.gov/cber/gdlns/comptest.pdf.

12. United States Pharmacopoeia (USP), Chapter <71> Sterility Tests, 23rd Edition, 1995, http://www.usp.org.

13. ICH Guidance on Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin, (63 FR 51074, September 24, 1998), http://www.fda.gov/cber/gdlns/virsafe.pdf.

14. ICH Topic Q3. Impurities.
Guidance for Industry: Q3A Impurities in New Drug Substances, February 2003, http://www.fda.gov/cber/gdlns/ichq3a.pdf.
Guidance for Industry: Q3B(R2) Impurities in New Drug Products, July 2006, http://www.fda.gov/cber/gdlns/ichq3br.pdf.
Guidance for Industry: Q3C Impurities: Residual Solvents, December 1997, http://www.fda.gov/cber/gdlns/q3cresolvent.pdf.

15. Guideline on Validation of the Limulus Amebocyte Lysate test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices, 1987, http://www.fda.gov/cber/gdlns/lal.pdf.

16. Guideline for Industry: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, July 1996 (ICH Q5C), http://www.fda.gov/cder/guidance/ichq5c.pdf.

17. Guidance for Industry: Q1A(R2): Stability Testing of New Drug Substances and Products (Revision 2), November 2003, http://www.fda.gov/cber/gdlns/ichstab.pdf.

18. Guidance for Industry: Q1E: Evaluation of Stability Data, June, 2004, http://www.fda.gov/cber/gdlns/ichstabdta.pdf.

19. Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics; Chemistry, Manufacturing, and Controls Documentation, May 1999, http://www.fda.gov/cber/gdlns/cntanr.pdf.

20. Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, Questions and Answers, May 2002, http://www.fda.gov/cber/gdlns/cntanrq&a.pdf.

21. Guidance for Industry: Environmental assessment of Human Drug and Biologics Applications, Revision 1, July 1998, http://www.fda.gov/cber/gdlns/environ.pdf.

22. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, September 2004, http://www.fda.gov/cber/gdlns/steraseptic.htm.

23. Manual of Standard Operating Procedures and Policies Investigational New Drug; Issuance of and Response to Clinical Hold Letters for Investigational New Drug Applications, SOPP 8201, Version #3, April 27, 1999, http://www.fda.gov/cber/regsopp/8201.htm.

APPENDIX A – PRODUCT REVIEW TEMPLATE (SOMATIC CELL THERAPY)

Supervisor Concurrence/Date

IND: XXXX

Sponsor's Submission Date: Month DD, YYYY
30 Day Review Due Date: Month DD, YYYY
STATUS: Pending

DATE: Month DD, YYYY

REVIEWER: Your Name
Your Title, OCTGT/DCGT/Your Branch

THROUGH: Branch Chief Name
Branch Chief, OCTGT/DCGT/Branch

SPONSOR:
Name:
Address:
Title:
Phone:
Fax:

SPONSOR POINT OF CONTACT:
Name:
Address:
Title:
Phone:
Fax:

TITLE OF IND:

PROPOSED USE:

REVIEW TEAM:
Clinical:
Pharm-Tox:
RPM:
Consults:

PRODUCT DESCRIPTION:

PHASE OF STUDY:

CROSS-REFERENCED INDS, IDES, MFS:

KEY WORDS:

INTRODUCTION / RATIONALE:

STUDY OBJECTIVES:

PRODUCT MANUFACTURING AND CHARACTERIZATION:

Product Manufacturing - Components

Cells

Allogeneic or Autologous Cell Components

Cell Source:

Method of Collection:

Donor Screening:
Description

Tabulation of Testing

Cell Bank System - If Applicable

Master Cell Bank (MCB)
Description

Tabulation of Testing

Working Cell Bank (WCB)
Description

Tabulation of Testing

Reagents

Tabulation of Reagents Used in Manufacture

Reagent/Excipient	Concentration at use	Source	Grade	Vendor	COA

Qualification Program

Determination of Removal of Reagents from Final Product

Combination Products - If Applicable

Drug or Device Components - If Applicable

Consult Review Issues:

Areas of Concern for Components:

Product Manufacturing - Procedures

Preparation of Autologous or Allogeneic Cells

Method of Cell Collection/Processing/Culture Conditions

Irradiation - If Applicable

Process Timing & Intermediate Storage

Final Harvest

Timing/Methods/Wash Procedure

Final Formulation

Formulation/Infusion Buffer

Excipients

Cell Density/Concentration in the Final Product
Storage Method Prior to Use

Areas of Concern for Manufacturing

PRODUCT TESTING

In-Process Testing and Criteria

Tabulation of Tests, Manufacturing Step, Test Methods, Criteria, and Test Sensitivity & Specificity

Test	Manufacturing Step Where Performed	Method	Criteria	Sensitivity	Specificity
Sterility					
Mycoplasma					
Purity (endotoxin)					
Purity (other contaminants)					
Identity					
Potency					
Others (cell dose)					
Others (cell viability)					

Description of Test Methods

FINAL PRODUCT RELEASE CRITERIA/SPECIFICATIONS

Tabulation of Final Product Release Criteria Tests, Test Methods, Criteria, Test Sensitivity & Specificity

Test	Method	Criteria	Sensitivity	Specificity	Results Available Prior to Release

Description of Test Methods

PRODUCT STABILITY

In-Process Stability Testing

Cryopreserved Cells

Other Intermediate Holding Steps

Final Product Stability Testing

Product Formulation to Patient Infusion

Shipping Conditions

OTHER ISSUES

Product Tracking

Labeling and Containers

In-Process Labeling

Final Product Labeling

Container Closure & Integrity

Environmental Impact

Validation and Qualification of the Manufacturing Process

QA/QC Program

Manufacturing Process Validation

Biostatistics

PRECLINICAL STUDIES

CLINICAL STUDIES

Protocol Title

Subject Population

Route of Administration

Dose

Frequency

Genetic, Biochemical, and Immunological Testing

Informed Consent

RECOMMENDATION

COMMENTS TO SPONSOR

Clinical Hold
Non-Clinical Hold

Signature Date:_____
Reviewer Name

APPENDIX B – CONSIDERATIONS FOR DEVELOPMENT OF FINAL PRODUCT RELEASE CRITERIA SPECIFICATIONS AND STABILITY PROTOCOLS

Specifications are the quality standards (i.e., tests, analytical procedures, and acceptance criteria) that confirm the quality of products and other materials used in the production of a product. Acceptance criteria are the numerical limits, ranges, or other criteria for the tests described. For additional information, see ICH Guideline Q6B: "Test Procedures and Acceptance Criteria for Biotechnological/Biological Products".[3] We believe that certain release specifications, such as those related to product safety, should be in place prior to initiating Phase 1 clinical studies. As product development proceeds, additional specifications for product quality and manufacturing consistency are developed and implemented. For additional discussion of manufacturing quality control, see "Guidance for Industry: Guideline on the Preparation of Investigational New Drug Products"[4] and "Guidance for Industry: IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing and Controls Information".[5]

A. Development of Release Acceptance Criteria

We recommend that proposed release acceptance criteria for the final product be based on scientific data and manufacturing experience obtained during development of the product as described below:

- Phase 1 – Based on data from lots used in preclinical studies.
- Phase 2 – Refine and tighten based on data generated during Phase 1.
- Phase 3 – Based on information collected during product development.
- Licensure – Based on information collected during product development using validated assays.

B. Development of Acceptance Criteria Analytical Procedures

We recommend that proposed analytical procedures be based on scientific data and manufacturing experience as described below:

- Phase 1-3 – Usually based on Code of Federal Regulation (CFR) methods or alternative methods, if appropriate.
- Phase 2 – If an alternative to the CFR method is used, we recommend that the sponsor initiate validation of the alternative by Phase 3.
- Licensure – The product specification should be in place and established under a validated assay.

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[3] Guidance for Industry: Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, August 1999, http://www.fda.gov/cder/guidance/Q6Bfnl.pdf.

[4] Guidance for Industry: Guideline on the Preparation of Investigational New Drug Products (Human and Animal), dated March 1991, reprinted November 1992, http://www.fda.gov/cder/guidance/old042fn.pdf.

[5] Guidance for Industry: IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing and Controls Information, May 2001, http://www.fda.gov/cber/gdlns/ind052501.htm

C. Development of Stability Protocols

In order to develop adequate stability data for timely submission in a license application, we recommend that a sponsor implement and expand the stability program as described below:

- Phase 1 - 3 – Preliminary data on product stability must indicate whether the product or components are likely to remain stable for the duration of the clinical trial. Note: the regulations require that the IND contain these data at each stage of the clinical trial (21 CFR 312.23(a)(7)(ii)).
- Phase 2 – We recommend that the sponsor initiate a stability protocol to accumulate additional data.
- Phase 3 – We recommend that the sponsor begin to establish the dating period, storage conditions, and shipping conditions based on data derived from the stability protocol.

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee [1],

After consulting the Committee of the Regions,

Acting in accordance with the procedure laid down in Article 251 of the Treaty [2],

Whereas:

(1) New scientific progress in cellular and molecular biotechnology has led to the development of advanced therapies, such as gene therapy, somatic cell therapy, and tissue engineering. This nascent field of biomedicine offers new opportunities for the treatment of diseases and dysfunctions of the human body.

(2) Insofar as advanced therapy products are presented as having properties for treating or preventing diseases in human beings, or that they may be used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting principally a pharmacological, immunological or metabolic action, they are biological medicinal products within the meaning of Annex I to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [3], read in conjunction with the definition of medicinal products in Article 1(2) thereof. Thus, the essential aim of any rules governing their production, distribution and use must be to safeguard public health.

(3) For reasons of clarity, complex therapeutic products require precise legal definitions. Gene therapy medicinal products and somatic cell therapy medicinal products have been defined in Annex I to Directive 2001/83/EC, but a legal definition of tissue engineered products remains to be laid down. When products are based on viable cells or tissues, the pharmacological, immunological or metabolic action should be considered as the principal mode of action. It should also be clarified that products which do not meet the definition of a medicinal product, such as products made exclusively of non-viable materials which act primarily by physical means, cannot by definition be advanced therapy medicinal products.

(4) According to Directive 2001/83/EC and the Medical Device Directives the basis for deciding which regulatory regime is applicable to combinations of medicinal products and medical devices is the principal mode of action of the combination product. However, the complexity of combined advanced therapy medicinal products containing viable cells or tissues requires a specific approach. For these products, whatever the role of the medical device, the pharmacological, immunological or metabolic action of these cells or tissues should be considered to be the principal mode of action of the combination product. Such combination products should always be regulated under this Regulation.

(5) Because of the novelty, complexity and technical specificity of advanced therapy medicinal products, specially tailored and harmonised rules are needed to ensure the free movement of those products within the Community, and the effective operation of the internal market in the biotechnology sector.

(6) This Regulation is a *lex specialis*, which introduces additional provisions to those laid down in Directive 2001/83/EC. The scope of this Regulation should be to regulate advanced therapy medicinal products which are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, in accordance with the general scope of the Community pharmaceutical legislation laid down in Title II of Directive 2001/83/EC. Advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Regulation whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined.

[1] OJ C 309, 16.12.2006, p. 15.

[2] Opinion of the European Parliament of 25 April 2007 (not yet published in the Official Journal) and Council Decision of 30 October 2007.

[3] OJ L 311, 28.11.2001, p. 67. Directive as last amended by Regulation (EC) No 1901/2006 (OJ L 378, 27.12.2006, p. 1).

(7) The regulation of advanced therapy medicinal products at Community level should not interfere with decisions made by Member States on whether to allow the use of any specific type of human cells, such as embryonic stem cells, or animal cells. It should also not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products containing, consisting of or derived from these cells.

(8) This Regulation respects the fundamental rights and observes the principles reflected in the Charter of Fundamental Rights of the European Union and also takes into account the Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine.

(9) All other modern biotechnology medicinal products currently regulated at Community level are already subject to a centralised authorisation procedure, involving a single scientific evaluation of the quality, safety and efficacy of the product, which is carried out to the highest possible standard by the European Medicines Agency as established by Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use [1] (hereinafter referred to as the Agency). This procedure should also be compulsory for advanced therapy medicinal products in order to overcome the scarcity of expertise in the Community, ensure a high level of scientific evaluation of these medicinal products in the Community, preserve the confidence of patients and medical professions in the evaluation and facilitate Community market access for these innovative technologies.

(10) The evaluation of advanced therapy medicinal products often requires very specific expertise, which goes beyond the traditional pharmaceutical field and covers areas bordering on other sectors such as biotechnology and medical devices. For this reason, it is appropriate to create, within the Agency, a Committee for Advanced Therapies, which should be responsible for preparing a draft opinion on the quality, safety and efficacy of each advanced therapy medicinal product for final approval by the Agency's Committee for Medicinal Products for Human Use. In addition, the Committee for Advanced Therapies should be consulted for the evaluation of any other medicinal product which requires specific expertise falling within its area of competence.

(11) The Committee for Advanced Therapies should gather the best available expertise on advanced therapy medicinal products in the Community. The composition of the Committee for Advanced Therapies should ensure appropriate coverage of the scientific areas relevant to advanced therapies, including gene therapy, cell therapy, tissue engineering, medical devices, pharmacovigilance and ethics. Patient associations and clinicians with scientific experience of advanced therapy medicinal products should also be represented.

(12) To ensure scientific consistency and the efficiency of the system, the Agency should ensure the coordination between the Committee for Advanced Therapies and its other Committees, advisory groups and working parties, notably the Committee for Medicinal Products for Human Use, the Committee on Orphan Medicinal Products, and the Scientific Advice Working Party.

(13) Advanced therapy medicinal products should be subject to the same regulatory principles as other types of biotechnology medicinal products. However, technical requirements, in particular the type and amount of quality, preclinical and clinical data necessary to demonstrate the quality, safety and efficacy of the product, may be highly specific. While those requirements are already laid down in Annex I to Directive 2001/83/EC for gene therapy medicinal products and somatic cell therapy medicinal products, they need to be established for tissue engineered products. This should be done through a procedure that provides for sufficient flexibility, so as to easily accommodate the rapid evolution of science and technology.

(14) Directive 2004/23/EC of the European Parliament and of the Council [2] sets standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. This Regulation should not derogate from the basic principles laid down in Directive 2004/23/EC, but should supplement them with additional requirements, where appropriate. Where an advanced therapy medicinal product contains human cells or tissues, Directive 2004/23/EC should apply only as far as donation, procurement and testing are concerned, since the further aspects are covered by this Regulation.

(15) As regards the donation of human cells or tissues, principles such as the anonymity of both donor and recipient, altruism of the donor and solidarity between donor and recipient should be respected. As a matter of principle, human cells or tissues contained in advanced therapy medicinal products should be procured from voluntary and unpaid donation. Member States should be urged to take all necessary steps to encourage a strong public and non-profit sector involvement in the procurement of human cells or tissues, as voluntary and unpaid cell and tissue donations may contribute to high safety standards for cells and tissues and therefore to the protection of human health.

[1] OJ L 136, 30.4.2004, p. 1. Regulation as amended by Regulation (EC) No 1901/2006.

[2] OJ L 102, 7.4.2004, p. 48.

(16) Clinical trials on advanced therapy medicinal products should be conducted in accordance with the overarching principles and the ethical requirements laid down in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [1]. However, Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products [2] should be adapted by laying down rules tailored to fully take into account the specific technical characteristics of advanced therapy medicinal products.

(17) The manufacture of advanced therapy medicinal products should be in compliance with the principles of good manufacturing practice, as set out in Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use [3], and adapted, where necessary, to reflect the specific nature of those products. Furthermore, guidelines specific to advanced therapy medicinal products should be drawn up, so as to properly reflect the particular nature of their manufacturing process.

(18) Advanced therapy medicinal products may incorporate medical devices or active implantable medical devices. Those devices should meet the essential requirements laid down in Council Directive 93/42/EEC of 14 June 1993 concerning medical devices [4] and Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices [5], respectively, in order to ensure an appropriate level of quality and safety. The results of the assessment of the medical device part or the active implantable medical device part by a notified body in accordance with those Directives should be recognised by the Agency in the evaluation of a combined advanced therapy medicinal product carried out under this Regulation.

(19) The requirements in Directive 2001/83/EC as regards the summary of product characteristics, labelling and the package leaflet should be adapted to the technical specificities of advanced therapy medicinal products by laying down specific rules on those products. These rules should comply fully with the patient's right to know the origin of any cells or tissues used in the preparation of advanced therapy medicinal products, while respecting donor anonymity.

(20) Follow-up of efficacy and adverse reactions is a crucial aspect of the regulation of advanced therapy medicinal products. The applicant should therefore detail in its marketing authorisation application whether measures are envisaged to ensure such follow-up and, if so, what those measures are. Where justified on public health grounds, the holder of the marketing authorisation should also be required to put in place a suitable risk management system to address risks related to advanced therapy medicinal products.

(21) The operation of this Regulation requires the establishment of guidelines to be drawn up either by the Agency or by the Commission. Open consultation with all interested parties, in particular Member State authorities and the industry, should be carried out in order to allow a pooling of the limited expertise in this area and ensure proportionality. The guidelines on good clinical practice and good manufacturing practice should be laid down as soon as possible, preferably during the first year after entry into force and before the date of application of this Regulation.

(22) A system allowing complete traceability of the patient as well as of the product and its starting materials is essential to monitor the safety of advanced therapy medicinal products. The establishment and maintenance of that system should be done in such a way as to ensure coherence and compatibility with traceability requirements laid down in Directive 2004/23/EC in respect of human tissues and cells, and in Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components [6]. The traceability system should also respect the provisions laid down in Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and the free movement of such data [7].

(23) As science evolves very rapidly in this field, undertakings developing advanced therapy medicinal products should be enabled to request scientific advice from the Agency, including advice on post-authorisation activities. As an incentive, the fee for that scientific advice should be kept at a minimal level for small and medium-sized enterprises, and should also be reduced for other applicants.

[1] OJ L 121, 1.5.2001, p. 34. Directive as amended by Regulation (EC) No 1901/2006.

[2] OJ L 91, 9.4.2005, p. 13.

[3] OJ L 262, 14.10.2003, p. 22.

[4] OJ L 169, 12.7.1993, p. 1. Directive as last amended by Directive 2007/47/EC of the European Parliament and of the Council (OJ L 247, 21.9.2007, p. 21).

[5] OJ L 189, 20.7.1990, p. 17. Directive as last amended by Directive 2007/47/EC.

[6] OJ L 33, 8.2.2003, p. 30.

[7] OJ L 281, 23.11.1995, p. 31. Directive as amended by Regulation (EC) No 1882/2003 (OJ L 284, 31.10.2003, p. 1).

(24) The Agency should be empowered to give scientific recommendations on whether a given product based on genes, cells or tissues meets the scientific criteria which define advanced therapy medicinal products, in order to address, as early as possible, questions of borderline with other areas such as cosmetics or medical devices, which may arise as science develops. The Committee for Advanced Therapies, with its unique expertise, should have a prominent role in the provision of such advice.

(25) Studies necessary to demonstrate the quality and non-clinical safety of advanced therapy medicinal products are often carried out by small and medium-sized enterprises. As an incentive to conduct those studies, a system of evaluation and certification of the resulting data by the Agency, independently of any marketing authorisation application, should be introduced. Even though the certification would not be legally binding, this system should also aim at facilitating the evaluation of any future application for clinical trials and marketing authorisation application based on the same data.

(26) 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 applications for marketing authorisation of advanced therapy medicinal products, the summary of product characteristics, labelling, and the package leaflet. The Commission should ensure that relevant information on envisaged measures is made available to interested parties without delay.

(27) Provisions should be laid down to report on the implementation of this Regulation after experience has been gained, with a particular attention to the different types of advanced therapy medicinal products authorised.

(28) The opinions of the Scientific Committee for Medicinal Products and Medical Devices concerning tissue engineering and that of the European Group on Ethics in Science and New Technologies have been taken into account, as well as international experience in this field.

(29) The measures necessary for the implementation of this Regulation should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission [1].

(30) In particular, the Commission should be empowered to adopt amendments to Annexes I to IV to this Regulation and to Annex I to Directive 2001/83/EC. Since those measures are of general scope and are designed to amend non-essential elements of this Regulation and of Directive 2001/83/EC, they must be adopted in accordance with the regulatory procedure with scrutiny provided for in Article 5a of Decision 1999/468/EC. Those measures are essential for the proper operation of the whole regulatory framework and should therefore be adopted as soon as possible.

(31) Directive 2001/83/EC and Regulation (EC) No 726/2004 should therefore be amended accordingly,

HAVE ADOPTED THIS REGULATION:

CHAPTER 1

SUBJECT MATTER AND DEFINITIONS

Article 1

Subject matter

This Regulation lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

Article 2

Definitions

1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

(a) 'Advanced therapy medicinal product' means any of the following medicinal products for human use:

— a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a tissue engineered product as defined in point (b).

(b) 'Tissue engineered product' means a product that:

— contains or consists of engineered 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.

A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.

[1] OJ L 184, 17.7.1999, p. 23. Decision as amended by Decision 2006/512/EC (OJ L 200, 22.7.2006, p. 11).

Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

(c) Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:

— the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,

— the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

(d) 'Combined advanced therapy medicinal product' means an advanced therapy medicinal product that fulfils the following conditions:

— it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and

— its cellular or tissue part must contain viable cells or tissues, or

— its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

2. Where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product.

3. An advanced therapy medicinal product containing both autologous (emanating from the patient himself) and allogeneic (coming from another human being) cells or tissues shall be considered to be for allogeneic use.

4. A product which may fall within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product shall be considered as a tissue engineered product.

5. A product which may fall within the definition of:

— a somatic cell therapy medicinal product or a tissue engineered product, and

— a gene therapy medicinal product,

shall be considered as a gene therapy medicinal product.

CHAPTER 2

MARKETING AUTHORISATION REQUIREMENTS

Article 3

Donation, procurement and testing

Where an advanced therapy medicinal product contains human cells or tissues, the donation, procurement and testing of those cells or tissues shall be made in accordance with Directive 2004/23/EC.

Article 4

Clinical trials

1. The rules set out in Article 6(7) and Article 9(4) and (6) of Directive 2001/20/EC in respect of gene therapy and somatic cell therapy medicinal products shall apply to tissue engineered products.

2. The Commission shall, after consulting the Agency, draw up detailed guidelines on good clinical practice specific to advanced therapy medicinal products.

Article 5

Good manufacturing practice

The Commission shall, after consulting the Agency, draw up guidelines in line with the principles of good manufacturing practice and specific to advanced therapy medicinal products.

Article 6

Issues specific to medical devices

1. A medical device which forms part of a combined advanced therapy medicinal product shall meet the essential requirements laid down in Annex I to Directive 93/42/EEC.

2. An active implantable medical device which forms part of a combined advanced therapy medicinal product shall meet the essential requirements laid down in Annex 1 to Directive 90/385/EEC.

Article 7

Specific requirements for advanced therapy medicinal products containing devices

In addition to the requirements laid down in Article 6(1) of Regulation (EC) No 726/2004, applications for the authorisation of an advanced therapy medicinal product containing medical devices, bio-materials, scaffolds or matrices shall include a description of the physical characteristics and performance of the product and a description of the product design methods, in accordance with Annex I to Directive 2001/83/EC.

CHAPTER 3

MARKETING AUTHORISATION PROCEDURE

Article 8

Evaluation procedure

1. The Committee for Medicinal Products for Human Use shall consult the Committee for Advanced Therapies on any scientific assessment of advanced therapy medicinal products necessary to draw up the scientific opinions referred to in Article 5(2) and (3) of Regulation (EC) No 726/2004. The Committee for Advanced Therapies shall also be consulted in the event of re-examination of the opinion pursuant to Article 9(2) of Regulation (EC) No 726/2004.

2. When preparing a draft opinion for final approval by the Committee for Medicinal Products for Human Use, the Committee for Advanced Therapies shall endeavour to reach a scientific consensus. If such consensus cannot be reached, the Committee for Advanced Therapies shall adopt the position of the majority of its members. The draft opinion shall mention the divergent positions and the grounds on which they are based.

3. The draft opinion given by the Committee for Advanced Therapies under paragraph 1 shall be sent to the Chairman of the Committee for Medicinal Products for Human Use in a timely manner so as to ensure that the deadline laid down in Article 6(3) or Article 9(2) of Regulation (EC) No 726/2004 can be met.

4. Where the scientific opinion on an advanced therapy medicinal product drawn up by the Committee for Medicinal Products for Human Use under Article 5(2) and (3) of Regulation (EC) No 726/2004 is not in accordance with the draft opinion of the Committee for Advanced Therapies, the Committee for Medicinal Products for Human Use shall annex to its opinion a detailed explanation of the scientific grounds for the differences.

5. The Agency shall draw up specific procedures for the application of paragraphs 1 to 4.

Article 9

Combined advanced therapy medicinal products

1. Where a combined advanced therapy medicinal product is concerned, the whole product shall be subject to final evaluation by the Agency.

2. The application for a marketing authorisation for a combined advanced therapy medicinal product shall include evidence of conformity with the essential requirements referred to in Article 6.

3. The application for a marketing authorisation for a combined advanced therapy medicinal product shall include, where available, the results of the assessment by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC of the medical device part or active implantable medical device part.

The Agency shall recognise the results of that assessment in its evaluation of the medicinal product concerned.

The Agency may request the relevant notified body to transmit any information related to the results of its assessment. The notified body shall transmit the information within a period of one month.

If the application does not include the results of the assessment, the Agency shall seek an opinion on the conformity of the device part with Annex I to Directive 93/42/EEC or Annex 1 to Directive 90/385/EEC from a notified body identified in conjunction with the applicant, unless the Committee for Advanced Therapies advised by its experts for medical devices decides that involvement of a notified body is not required.

CHAPTER 4

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Article 10

Summary of product characteristics

By way of derogation from Article 11 of Directive 2001/83/EC, the summary of the product characteristics for advanced therapy medicinal products shall contain the information listed in Annex II to this Regulation, in the order indicated therein.

Article 11

Labelling of outer/immediate packaging

By way of derogation from Articles 54 and 55(1) of Directive 2001/83/EC, the particulars listed in Annex III to this Regulation shall appear on the outer packaging of advanced therapy medicinal products or, where there is no outer packaging, on the immediate packaging.

Article 12

Special immediate packaging

In addition to the particulars mentioned in Article 55(2) and (3) of Directive 2001/83/EC, the following particulars shall appear on the immediate packaging of advanced therapy medicinal products:

(a) the unique donation and product codes, as referred to in Article 8(2) of Directive 2004/23/EC;

(b) in the case of advanced therapy medicinal products for autologous use, the unique patient identifier and the statement 'For autologous use only'.

Article 13

Package leaflet

1. By way of derogation from Article 59(1) of Directive 2001/83/EC, the package leaflet for an advanced therapy medicinal product shall be drawn up in accordance with the summary of product characteristics and shall include the information listed in Annex IV to this Regulation, in the order indicated therein.

2. The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.

CHAPTER 5

POST-AUTHORISATION REQUIREMENTS

Article 14

Post-authorisation follow-up of efficacy and adverse reactions, and risk management

1. In addition to the requirements for pharmacovigilance laid down in Articles 21 to 29 of Regulation (EC) No 726/2004, the applicant shall detail, in the marketing authorisation application, the measures envisaged to ensure the follow-up of efficacy of advanced therapy medicinal products and of adverse reactions thereto.

2. Where there is particular cause for concern, the Commission shall, on the advice of the Agency, require as part of the marketing authorisation that a risk management system designed to identify, characterise, prevent or minimise risks related to advanced therapy medicinal products, including an evaluation of the effectiveness of that system, be set up, or that specific post-marketing studies be carried out by the holder of the marketing authorisation and submitted for review to the Agency.

In addition, the Agency may request submission of additional reports evaluating the effectiveness of any risk management system and the results of any such studies performed.

Evaluation of the effectiveness of any risk management system and the results of any studies performed shall be included in the periodic safety update reports referred to in Article 24(3) of Regulation (EC) No 726/2004.

3. The Agency shall forthwith inform the Commission if it finds that the marketing authorisation holder has failed to comply with the requirements referred to in paragraph 2.

4. The Agency shall draw up detailed guidelines relating to the application of paragraphs 1, 2 and 3.

5. If serious adverse events or reactions occur in relation to a combined advanced therapy medicinal product, the Agency shall inform the relevant national competent authorities responsible for implementing Directives 90/385/EEC, 93/42/EEC and 2004/23/EC.

Article 15

Traceability

1. The holder of a marketing authorisation for an advanced therapy medicinal product shall establish and maintain a system ensuring that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used.

2. The hospital, institution or private practice where the advanced therapy medicinal product is used shall establish and maintain a system for patient and product traceability. That system shall contain sufficient detail to allow linking of each product to the patient who received it and vice versa.

3. Where an advanced therapy medicinal product contains human cells or tissues, the marketing authorisation holder, as well as the hospital, institution or private practice where the product is used, shall ensure that the traceability systems established in accordance with paragraphs 1 and 2 of this Article are complementary to, and compatible with, the requirements laid down in Articles 8 and 14 of Directive 2004/23/EC as regards human cells and tissues other than blood cells, and Articles 14 and 24 of Directive 2002/98/EC as regards human blood cells.

4. The marketing authorisation holder shall keep the data referred to in paragraph 1 for a minimum of 30 years after the expiry date of the product, or longer if required by the Commission as a term of the marketing authorisation.

5. In case of bankruptcy or liquidation of the marketing authorisation holder, and in the event that the marketing authorisation is not transferred to another legal entity, the data referred to in paragraph 1 shall be transferred to the Agency.

6. In the event that the marketing authorisation is suspended, revoked or withdrawn, the holder of the marketing authorisation shall remain subject to the obligations laid down in paragraphs 1, 3 and 4.

7. The Commission shall draw up detailed guidelines relating to the application of paragraphs 1 to 6, in particular the type and amount of data referred to in paragraph 1.

CHAPTER 6

INCENTIVES

Article 16

Scientific advice

1. The applicant or holder of a marketing authorisation may request advice from the Agency on the design and conduct of pharmacovigilance and of the risk management system referred to in Article 14.

2. By way of derogation from Article 8(1) of Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products [1], a 90 % reduction for small and medium-sized enterprises and 65 % for other applicants shall apply to the fee for scientific advice payable to the Agency for any advice given in respect of advanced therapy medicinal products pursuant to paragraph 1 of this Article and Article 57(1)(n) of Regulation (EC) No 726/2004.

Article 17

Scientific recommendation on advanced therapy classification

1. Any applicant developing a product based on genes, cells or tissues may request a scientific recommendation of the Agency with a view to determining whether the referred product falls, on scientific grounds, within the definition of an advanced therapy medicinal product. The Agency shall deliver this recommendation after consultation with the Commission and within 60 days after receipt of the request.

2. The Agency shall publish summaries of the recommendations delivered in accordance with paragraph 1, after deletion of all information of commercial confidential nature.

Article 18

Certification of quality and non-clinical data

Small and medium-sized enterprises developing an advanced therapy medicinal product may submit to the Agency all relevant quality and, where available, non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC, for scientific evaluation and certification.

The Commission shall lay down provisions for the evaluation and certification of such data, in accordance with the regulatory procedure referred to in Article 26(2).

Article 19

Reduction of the fee for marketing authorisation

1. By way of derogation from Regulation (EC) No 297/95, the fee for marketing authorisation shall be reduced by 50 % if the applicant is a hospital or a small or medium-sized enterprise and can prove that there is a particular public health interest in the Community in the advanced therapy medicinal product concerned.

2. Paragraph 1 shall also apply to fees charged by the Agency for post-authorisation activities in the first year following the granting of the marketing authorisation for the advanced therapy medicinal product.

3. Paragraphs 1 and 2 shall apply during the transitional periods laid down in Article 29.

CHAPTER 7

COMMITTEE FOR ADVANCED THERAPIES

Article 20

Committee for Advanced Therapies

1. A Committee for Advanced Therapies shall be established within the Agency.

2. Save where otherwise provided in this Regulation, Regulation (EC) No 726/2004 shall apply to the Committee for Advanced Therapies.

3. The Executive Director of the Agency shall ensure appropriate coordination between the Committee for Advanced Therapies and the other Committees of the Agency, in particular the Committee for Medicinal Products for Human Use and the Committee for Orphan Medicinal Products, their working parties and any other scientific advisory groups.

Article 21

Composition of the Committee for Advanced Therapies

1. The Committee for Advanced Therapies shall be composed of the following members:

(a) five members or co-opted members of the Committee for Medicinal Products for Human Use from five Member States, with alternates either proposed by their respective Member State or, in the case of co-opted members of the Committee for Medicinal Products for Human Use, identified by the latter on the advice of the corresponding co-opted member. These five members with their alternates shall be appointed by the Committee for Medicinal Products for Human Use;

(b) one member and one alternate appointed by each Member State whose national competent authority is not represented among the members and alternates appointed by the Committee for Medicinal Products for Human Use;

(c) two members and two alternates appointed by the Commission, on the basis of a public call for expressions of interest and after consulting the European Parliament, in order to represent clinicians;

[1] OJ L 35, 15.2.1995, p. 1. Regulation as last amended by Regulation (EC) No 1905/2005 (OJ L 304, 23.11.2005, p. 1).

(d) two members and two alternates appointed by the Commission, on the basis of a public call for expressions of interest and after consulting the European Parliament, in order to represent patients' associations.

The alternates shall represent and vote for the members in their absence.

2. All members of the Committee for Advanced Therapies shall be chosen for their scientific qualification or experience in respect of advanced therapy medicinal products. For the purposes of paragraph 1(b), the Member States shall cooperate, under the coordination of the Executive Director of the Agency, in order to ensure that the final composition of the Committee for Advanced Therapies provides appropriate and balanced coverage of the scientific areas relevant to advanced therapies, including medical devices, tissue engineering, gene therapy, cell therapy, biotechnology, surgery, pharmacovigilance, risk management and ethics.

At least two members and two alternates of the Committee for Advanced Therapies shall have scientific expertise in medical devices.

3. The members of the Committee for Advanced Therapies shall be appointed for a renewable period of three years. At meetings of the Committee for Advanced Therapies, they may be accompanied by experts.

4. The Committee for Advanced Therapies shall elect its Chairman from among its members for a term of three years, renewable once.

5. The names and scientific qualifications of all members shall be made public by the Agency, in particular on the Agency's website.

Article 22

Conflicts of interest

In addition to the requirements laid down in Article 63 of Regulation (EC) No 726/2004, members and alternates of the Committee for Advanced Therapies shall have no financial or other interests in the biotechnology sector and medical device sector that could affect their impartiality. All indirect interests that could relate to these sectors shall be entered in the register referred to in Article 63(2) of Regulation (EC) No 726/2004.

Article 23

Tasks of the Committee for Advanced Therapies

The Committee for Advanced Therapies shall have the following tasks:

(a) to formulate a draft opinion on the quality, safety and efficacy of an advanced therapy medicinal product for final approval by the Committee for Medicinal Products for Human Use and to advise the latter on any data generated in the development of such a product;

(b) to provide advice, pursuant to Article 17, on whether a product falls within the definition of an advanced therapy medicinal product;

(c) at the request of the Committee for Medicinal Products for Human Use, to advise on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in one of the scientific areas referred to in Article 21(2);

(d) to provide advice on any question related to advanced therapy medicinal products, at the request of the Executive Director of the Agency or the Commission;

(e) to assist scientifically in the elaboration of any documents related to the fulfilment of the objectives of this Regulation;

(f) at the Commission's request, to provide scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies which requires expertise in one of the scientific areas referred to in Article 21(2);

(g) to contribute to the scientific advice procedures referred to in Article 16 of this Regulation and in Article 57(1)(n) of Regulation (EC) No 726/2004.

CHAPTER 8

GENERAL AND FINAL PROVISIONS

Article 24

Adaptation of Annexes

The Commission shall, after consulting the Agency and in accordance with the regulatory procedure with scrutiny referred to in Article 26(3), amend Annexes I to IV in order to adapt them to scientific and technical evolution.

Article 25

Report and review

By 30 December 2012, the Commission shall publish a general report on the application of this Regulation, which shall include comprehensive information on the different types of advanced therapy medicinal products authorised pursuant to this Regulation.

In this report, the Commission shall assess the impact of technical progress on the application of this Regulation. It shall also review the scope of this Regulation, including in particular the regulatory framework for combined advanced therapy medicinal products.

Article 26

Committee procedure

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use set up by Article 121(1) of Directive 2001/83/EC.

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. Where reference is made to this paragraph, Article 5a(1) to (4) and Article 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

Article 27

Amendments to Regulation (EC) No 726/2004

Regulation (EC) No 726/2004 is hereby amended as follows:

1. in the first subparagraph of Article 13(1), the first sentence shall be replaced by the following:

   'Without prejudice to Article 4(4) and (5) of Directive 2001/83/EC, a marketing authorisation which has been granted in accordance with this Regulation shall be valid throughout the Community.';

2. Article 56 shall be amended as follows:

   (a) in paragraph 1, the following point shall be inserted:

   '(da) the Committee for Advanced Therapies;'

   (b) in the first sentence of the first subparagraph of paragraph 2, the words 'paragraph 1(a) to (d)' shall be replaced by 'paragraph 1(a) to (da)';

3. the Annex shall be amended as follows:

   (a) the following point shall be inserted:

   '1a. Advanced therapy medicinal products as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products (*).

   (*) OJ L 324, 10.12.2007, p. 121';

   (b) In point 3, the second subparagraph shall be replaced by the following:

   'After 20 May 2008, the Commission, having consulted the Agency, may present any appropriate proposal to amend this point and the European Parliament and the Council shall take a decision thereon in accordance with the Treaty.'

Article 28

Amendments to Directive 2001/83/EC

Directive 2001/83/EC is hereby amended as follows:

1. in Article 1, the following point shall be inserted:

   '4a. *Advanced therapy medicinal product:*

   A product as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products (*).

   (*) OJ L 324, 10.12.2007, p. 121';

2. in Article 3, the following point shall be added:

   '7. Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.

   Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (*).

   (*) OJ L 136, 30.4.2004, p. 1. Regulation as amended by Regulation (EC) No 1901/2006 (OJ L 378, 27.12.2006, p. 1).';

3. in Article 4, the following paragraph shall be added:

   '5. This Directive and all Regulations referred to therein shall not affect the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from these cells, on grounds not dealt with in the aforementioned Community legislation. The Member States shall communicate the national legislation concerned to the Commission. The Commission shall make this information publicly available in a register.';