(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.';

4. in Article 6(1), the first subparagraph shall be replaced by the following:

'No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1394/2007.'

Article 29

Transitional period

1. Advanced therapy medicinal products, other than tissue engineered products, which were legally on the Community market in accordance with national or Community legislation on 30 December 2008, shall comply with this Regulation no later than 30 December 2011.

2. Tissue engineered products which were legally on the Community market in accordance with national or Community legislation on 30 December 2008 shall comply with this Regulation no later than 30 December 2012.

3. By way of derogation from Article 3(1) of Regulation (EC) No 297/95, no fee shall be payable to the Agency in respect of applications submitted for the authorisation of the advanced therapy medicinal products mentioned in paragraphs 1 and 2 of this Article.

Article 30

Entry into force

This Regulation shall enter into force on the 20th day following its publication in the *Official Journal of the European Union.*

It shall apply from 30 December 2008.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Strasbourg, 13 November 2007.

For the European Parliament
The President
H.-G. PÖTTERING

For the Council
The President
M. LOBO ANTUNES

ANNEX I

Manipulations referred to in the first indent of Article 2(1)(c)

— cutting,

— grinding,

— shaping,

— centrifugation,

— soaking in antibiotic or antimicrobial solutions,

— sterilization,

— irradiation,

— cell separation, concentration or purification,

— filtering,

— lyophilization,

— freezing,

— cryopreservation,

— vitrification.

ANNEX II

Summary of product characteristics referred to in Article 10

1. Name of the medicinal product.

2. Composition of the product:

2.1. general description of the product, if necessary with explanatory drawings and pictures,

2.2. qualitative and quantitative composition in terms of the active substances and other constituents of the product, knowledge of which is essential for proper use, administration or implantation of the product. Where the product contains cells or tissues, a detailed description of these cells or tissues and of their specific origin, including the species of animal in cases of non-human origin, shall be provided,

For a list of excipients, see point 6.1.

3. Pharmaceutical form.

4. Clinical particulars:

4.1. therapeutic indications,

4.2. posology and detailed instructions for use, application, implantation or administration for adults and, where necessary, for children or other special populations, if necessary with explanatory drawings and pictures,

4.3. contra-indications,

4.4. special warnings and precautions for use, including any special precautions to be taken by persons handling such products and administering them to or implanting them in patients, together with any precautions to be taken by the patient,

4.5. interaction with other medicinal products and other forms of interactions,

4.6. use during pregnancy and lactation,

4.7. effects on ability to drive and to use machines,

4.8. undesirable effects,

4.9. overdose (symptoms, emergency procedures).

5. Pharmacological properties:

5.1. pharmacodynamic properties,

5.2. pharmacokinetic properties,

5.3. preclinical safety data.

6. Quality particulars:

6.1. list of excipients, including preservative systems,

6.2. incompatibilities,

6.3. shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,

6.4. special precautions for storage,

6.5. nature and contents of container and special equipment for use, administration or implantation, if necessary with explanatory drawings and pictures,

6.6. special precautions and instructions for handling and disposal of a used advanced therapy medicinal product or waste materials derived from such product, if appropriate and, if necessary, with explanatory drawings and pictures.

7. Marketing authorisation holder.

8. Marketing authorisation number(s).

9. Date of the first authorisation or renewal of the authorisation.

10. Date of revision of the text.

ANNEX III

Labelling of outer/immediate packaging referred to in Article 11

(a) The name of the medicinal product and, if appropriate, an indication of whether it is intended for babies, children or adults; the international non-proprietary name (INN) shall be included, or, if the product has no INN, the common name;

(b) A description of the active substance(s) expressed qualitatively and quantitatively, including, where the product contains cells or tissues, the statement 'This product contains cells of human/animal [as appropriate{] origin' together with a short description of these cells or tissues and of their specific origin, including the species of animal in cases of non-human origin;

(c) The pharmaceutical form and, if applicable, the contents by weight, by volume or by number of doses of the product;

(d) A list of excipients, including preservative systems;

(e) The method of use, application, administration or implantation and, if necessary, the route of administration. If applicable, space shall be provided for the prescribed dose to be indicated;

(f) A special warning that the medicinal product must be stored out of the reach and sight of children;

(g) Any special warning necessary for the particular medicinal product;

(h) The expiry date in clear terms (month and year; and day if applicable);

(i) Special storage precautions, if any;

(j) Specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products, where appropriate, as well as reference to any appropriate collection system in place;

(k) The name and address of the marketing authorisation holder and, where applicable, the name of the representative appointed by the holder to represent him;

(l) Marketing authorisation number(s);

(m) The manufacturer's batch number and the unique donation and product codes referred to in Article 8(2) of Directive 2004/23/EC;

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

ANNEX IV

Package leaflet referred to in Article 13

(a) For the identification of the advanced therapy medicinal product:

(i) the name of the advanced therapy medicinal product and, if appropriate, an indication of whether it is intended for babies, children or adults. The common name shall be included;

(ii) the therapeutic group or type of activity in terms easily understandable for the patient;

(iii) where the product contains cells or tissues, a description of those cells or tissues and of their specific origin, including the species of animal in cases of non-human origin;

(iv) where the product contains medical devices or active implantable medical devices, a description of those devices and their specific origin;

(b) The therapeutic indications;

(c) A list of information which is necessary before the medicinal product is taken or used, including:

(i) contra-indications;

(ii) appropriate precautions for use;

(iii) forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product;

(iv) special warnings;

(v) if appropriate, possible effects on the ability to drive vehicles or to operate machinery;

(vi) the excipients, knowledge of which is important for the safe and effective use of the medicinal product and which are included in the detailed guidance published pursuant to Article 65 of Directive 2001/83/EC.

The list shall also take into account the particular condition of certain categories of users, such as children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions;

(d) The necessary and usual instructions for proper use, and in particular:

(i) the posology;

(ii) the method of use, application, administration or implantation and, if necessary, the route of administration;

and, as appropriate, depending on the nature of the product:

(iii) the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;

(iv) the duration of treatment, where it should be limited;

(v) the action to be taken in case of an overdose (such as symptoms, emergency procedures);

(vi) information on what to do when one or more doses have not been taken;

(vii) a specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the product;

(e) A description of the adverse reactions which may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case; the patient should be expressly asked to communicate any adverse reaction which is not mentioned in the package leaflet to his doctor or pharmacist;

(f) A reference to the expiry date indicated on the label, with:

(i) a warning against using the product after that date;

(ii) where appropriate, special storage precautions;

(iii) if necessary, a warning concerning certain visible signs of deterioration;

(iv) the full qualitative and quantitative composition;

(v) the name and address of the marketing authorisation holder and, where applicable, the name of his appointed representatives in the Member States;

(vi) the name and address of the manufacturer;

(g) The date on which the package leaflet was last revised.

DIRECTIVES

COMMISSION DIRECTIVE 2009/120/EC

of 14 September 2009

amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard 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 [1], and in particular Article 120 thereof,

Whereas:

(1) Medicinal products for human use may only be placed on the market if a marketing authorisation has been delivered by a competent authority on the basis of an application dossier containing the results of tests and trials carried out on the products concerned.

(2) Annex I to Directive 2001/83/EC lays down detailed scientific and technical requirements regarding the testing of medicinal products for human use against which the quality, safety and efficacy of the medicinal product should be assessed. Those detailed scientific and technical requirements should be regularly adapted to take account of scientific and technical progress.

(3) Due to scientific and technical progress in the field of advanced therapies, as reflected in 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 [2], it is appropriate to adapt Annex I. The definitions and detailed scientific and technical requirements for gene therapy medicinal products and somatic cell therapy medicinal products should be updated. Moreover, detailed scientific and technical requirements should be established for tissue engineered products, as well as for advanced therapy medicinal product containing devices and combined advanced therapy medicinal products.

(4) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee for Medicinal Products for Human Use,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Part IV of Annex I to Directive 2001/83/EC is replaced by the text set out in the Annex to this Directive.

Article 2

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 5 April 2010 at the latest. They shall forthwith communicate to the Commission the text of those provisions and a correlation table between those provisions and this Directive.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 3

This Directive shall enter into force on the 20th day following its publication in the *Official Journal of the European Union.*

Article 4

This Directive is addressed to the Member States.

Done at Brussels, 14 September 2009.

For the Commission
Günter VERHEUGEN
Vice-President

[1] OJ L 311, 28.11.2001, p. 67.
[2] OJ L 324, 10.12.2007, p. 121.

ANNEX

'PART IV

ADVANCED THERAPY MEDICINAL PRODUCTS

1. INTRODUCTION

Marketing authorisation applications for advanced therapy medicinal products, as defined in point (a) of Article 2(1) of Regulation (EC) No 1394/2007, shall follow the format requirements (Modules 1, 2, 3, 4 and 5) described in Part I of this Annex.

The technical requirements for Modules 3, 4 and 5 for biological medicinal products, as described in Part I of this Annex, shall apply. The specific requirements for advanced therapy medicinal products described in sections 3, 4 and 5 of this part explain how the requirements in Part I apply to advanced therapy medicinal products. In addition, where appropriate and taking into account the specificities of advanced therapy medicinal products, additional requirements have been set.

Due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application, in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products referred to in point 4 of the "Introduction and general principles".

The risk analysis may cover the entire development. Risk factors that may be considered include: the origin of the cells (autologous, allogeneic, xenogeneic), the ability to proliferate and/or differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, the extent of replication competence of viruses or micro-organisms used *in vivo*, the level of integration of nucleic acids sequences or genes into the genome, the long time functionality, the risk of oncogenicity and the mode of administration or use.

Relevant available non-clinical and clinical data or experience with other, related advanced therapy medicinal products may also be considered in the risk analysis.

Any deviation from the requirements of this Annex shall be scientifically justified in Module 2 of the application dossier. The risk analysis described above, when applied, shall also be included and described in Module 2. In this case, the methodology followed, the nature of the identified risks and the implications of the risk based approach for the development and evaluation program shall be discussed and any deviations from the requirements of this Annex resulting from the risk analysis shall be described.

2. DEFINITIONS

For the purposes of this Annex, in addition to the definitions laid down in Regulation (EC) No 1394/2007, the definitions set out in sections 2.1 and 2.2 shall apply.

2.1. **Gene therapy medicinal product**

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

2.2. **Somatic cell therapy medicinal product**

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

3. SPECIFIC REQUIREMENTS REGARDING MODULE 3

3.1. **Specific requirements for all advanced therapy medicinal products**

A description of the traceability system that the marketing authorisation holder intends to establish and maintain to ensure 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, shall be provided.

The traceability system shall be complementary to, and compatible with, the requirements established in Directive 2004/23/EC of the European Parliament and of the Council (*), as regards human cells and tissues other than blood cells, and Directive 2002/98/EC, as regards human blood cells.

3.2. **Specific requirements for gene therapy medicinal products**

3.2.1. *Introduction: finished product, active substance and starting materials*

3.2.1.1. Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified micro-organism(s) or virus(es)

The finished medicinal product shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.

The active substance shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).

3.2.1.2. Gene therapy medicinal product containing genetically modified cells

The finished medicinal product shall consist of genetically modified cells formulated in the final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.

The active substance shall consist of cells genetically modified by one of the products described in section 3.2.1.1 above.

3.2.1.3. In the case of products consisting of viruses or viral vectors, the starting materials shall be the components from which the viral vector is obtained, i.e. the master virus vector seed or the plasmids used to transfect the packaging cells and the master cell bank of the packaging cell line.

3.2.1.4. In the case of products consisting of plasmids, non-viral vectors and genetically modified microorganism(s) other than viruses or viral vectors, the starting materials shall be the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the master cell bank of recombinant microbial cells.

3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.

3.2.2. *Specific requirements*

In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:

(a) information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps;

(b) for products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the micro-organism or virus, pathogenicity and characteristics of the parental strain shall be provided;

(c) process-related impurities and product-related impurities shall be described in the relevant sections of the dossier, and in particular replication competent virus contaminants if the vector is designed to be replication incompetent;

(d) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;

(e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent freezing/storage procedures, shall be tested.

For genetically modified cells, in addition to the specific requirements for gene therapy medicinal products, the quality requirements for somatic cell therapy medicinal products and tissue engineered products (see section 3.3) shall apply.

3.3. **Specific requirements for somatic cell therapy medicinal products and tissue engineered products**

3.3.1. *Introduction: finished product, active substance and starting materials*

The finished medicinal product shall consist of the active substance formulated in its immediate container for the intended medical use, and in its final combination for combined advanced therapy medicinal products.

The active substance shall be composed of the engineered cells and/or tissues.

Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.

Materials used during the manufacture of the active substance (e.g. culture media, growth factors) and that are not intended to form part of the active substance shall be considered as raw materials.

3.3.2. *Specific requirements*

In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:

3.3.2.1. Starting materials

(a) Summary information shall be provided on donation, procurement and testing of the human tissue and cells used as starting materials and made in accordance with Directive 2004/23/EC. If non-healthy cells or tissues (e.g. cancer tissue) are used as starting materials, their use shall be justified.

(b) If allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described.

(c) The potential variability introduced through the human or animal tissues and cells shall be addressed as part of the validation of the manufacturing process, characterisation of the active substance and the finished product, development of assays, setting of specifications and stability.

(d) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents, including vertically transmitted micro-organisms and viruses, and evidence of the suitability of the animal facilities shall be provided.

(e) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of the transgenic animal shall be provided.

(f) For the genetic modification of the cells, the technical requirements specified in section 3.2 shall apply.

(g) The testing regimen of any additional substance (scaffolds, matrices, devices, biomaterials, biomolecules or other components), which are combined with engineered cells of which they form an integral part, shall be described and justified.

(h) For scaffolds, matrices and devices that fall under the definition of a medical device or active implantable medical device, the information required under section 3.4 for the evaluation of the combined advanced therapy medicinal product shall be provided.

3.3.2.2. Manufacturing process

(a) The manufacturing process shall be validated to ensure batch and process consistency, functional integrity of the cells throughout manufacturing and transport up to the moment of application or administration, and proper differentiation state.

(b) If cells are grown directly inside or on a matrix, scaffold or device, information shall be provided on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination.

3.3.2.3. Characterisation and control strategy

(a) Relevant information shall be provided on the characterisation of the cell population or cell mixture in terms of identity, purity (e.g. adventitious microbial agents and cellular contaminants), viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use. The genetic stability of the cells shall be demonstrated.

(b) Qualitative and, where possible, quantitative information on product- and process-related impurities, as well as on any material capable of introducing degradation products during production, shall be provided. The extent of the determination of impurities shall be justified.

(c) If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process testing, this shall be justified.

(d) Where biologically active molecules (such as growth factors, cytokines) are present as components of the cell-based product, their impact and interaction with other components of the active substance shall be characterised.

(e) Where a three-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated shall be part of the characterisation for these cell-based products. Where needed, non-clinical investigations shall complement the physicochemical characterisation.

3.3.2.4. Excipients

For excipient(s) used in cell or tissue-based medicinal products (e.g. the components of the transport medium), the requirements for novel excipients, as laid down in Part I of this Annex, shall apply, unless data exists on the interactions between the cells or tissues and the excipients.

3.3.2.5. Developmental studies

The description of the development program shall address the choice of materials and processes. In particular, the integrity of the cell population as in the final formulation shall be discussed.

3.3.2.6. Reference materials

A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised.

3.4. Specific requirements for advanced therapy medicinal products containing devices

3.4.1. *Advanced therapy medicinal product containing devices as referred to in Article 7 of Regulation (EC) No 1394/2007*

A description of the physical characteristics and performance of the product and a description of the product design methods shall be provided.