# COMMISSION REGULATION (EC) No 668/2009

## of 24 July 2009

## implementing Regulation (EC) No 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises

**(Text with EEA relevance)**

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to 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 [1], and in particular Article 18 thereof,

Whereas:

(1) It is appropriate, in the framework of Regulation (EC) No 1394/2007, to lay down provisions for the evaluation and certification of quality and non-clinical data submitted by small and medium-sized enterprises to the European Medicines Agency (hereinafter the Agency) in order to give those enterprises an incentive to conduct quality and non-clinical studies on advanced therapy medicinal products.

(2) For reasons of coherence and transparency, the definition of micro, small and medium-sized enterprises provided for in Commission Recommendation 2003/361/EC of 6 May 2003 concerning the definition of micro, small and medium-sized enterprises [2] should apply.

(3) Pursuant to Regulation (EC) No 1394/2007, the certification procedure should be independent from any application for marketing authorisation. Nevertheless, it should also aim at facilitating the evaluation of any future application for clinical trial and marketing authorisation based on the same data. For this reason, the evaluation of an application for certification should be conducted in accordance with the same scientific and technical requirements as those applicable to a marketing authorisation application, as laid down in 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].

(4) It should be possible for applicants for certification to provide all or parts of quality and non-clinical data required by Annex I to Directive 2001/83/EC. However, in order to ensure the added value of certifications, it is appropriate to lay down a minimum set of data required for certification.

(5) Within the Agency, the Committee for Advanced Therapies has the appropriate expertise for the examination of quality and non-clinical data relating to advanced therapy medicinal products. It should therefore be responsible for evaluating applications for certification.

(6) Where necessary, it should be possible for the Committee for Advanced Therapies to make completion of its evaluation subject to a site visit of the premises where the advanced therapy medicinal product is being developed.

(7) Applications for certification may relate to combined advanced therapy medicinal products within the meaning of Regulation (EC) No 1394/2007. In such a case, additional requirements should apply in relation to the conformity of the medical device or active implantable medical device contained in the combined product with 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.

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

[1] OJ L 324, 10.12.2007, p. 121.
[2] OJ L 124, 20.5.2003, p. 36.
[3] OJ L 311, 28.11.2001, p. 67.
[4] OJ L 169, 12.7.1993, p. 1.
[5] OJ L 189, 20.7.1990, p. 17.

HAS ADOPTED THIS REGULATION:

*Article 1*

**Scope**

This Regulation shall apply to micro, small and medium-sized enterprises, within the meaning of Recommendation 2003/361/EC, which develop an advanced-therapy medicinal product and are established in the Community.

*Article 2*

**Procedure for evaluation and certification**

1. Applications for the scientific evaluation and certification of quality and non-clinical data relating to an advanced therapy medicinal product shall be submitted to the Agency and shall contain the following:

(a) all information necessary to demonstrate that the applicant falls within the scope of this Regulation as set out in Article 1;

(b) an indication as to whether the application relates to quality data only or to quality and non-clinical data;

(c) a reference to any applications for certification previously submitted for the same advanced therapy medicinal product, an indication as to whether a certificate has been granted or not and an explanation of the added value of the new application and of the differences between the new application and the application previously submitted;

(d) the relevant fee as provided for in Council Regulation (EC) No 297/95 ([1]);

(e) the data referred to in module 3 of Part I of Annex I to Directive 2001/83/EC which is submitted for certification in accordance with the second subparagraph, taking into account the specific requirements laid down in Part IV of that Annex and the scientific guidelines referred to in Article 5.

(f) where the application relates to both quality data and non-clinical data, the data referred to in module 4 of Part I of Annex I to Directive 2001/83/EC which is submitted for certification in accordance with the third subparagraph, taking into account the specific requirements laid down in Part IV of that Annex and the scientific guidelines referred to in Article 5.

For the purposes of point (e) of the first subparagraph, the application shall contain at least the following data:

(a) general information and information related to the starting and raw materials;

(b) manufacturing process of the active substance(s), with the exception of data on process validation;

(c) characterisation of the active substance(s), limited to the data necessary to adequately describe the active substance(s);

(d) control of active substance(s), with the exception of data on the validation of the assays;

(e) description and composition of the finished product.

For the purposes of point (f) of the first subparagraph, the application shall contain at least the following data:

(a) primary pharmacodynamic data supporting the rationale for the proposed therapeutic use;

(b) pharmacokinetics bio-distribution data, if relevant to corroborate the primary pharmacodynamic data;

(c) at least one toxicity study.

2. If the application fulfils the requirements laid down in paragraph 1 the Agency shall acknowledge receipt of a valid application.

3. The Committee for Advanced Therapies shall evaluate the valid application within 90 days following its acknowledgment of receipt.

For the purposes of that evaluation, the Committee for Advanced Therapies shall, in particular with a view to the subsequent evaluation of any future application for clinical trial and marketing authorisation, determine whether:

(a) the quality data submitted and the quality testing methodology followed by the applicant comply with the scientific and technical requirements set out in sections 2.3 and 3 of Part I, in Part IV and, where relevant to quality data, in the Introduction and General Principles of Annex I to Directive 2001/83/EC;

([1]) OJ L 35, 15.2.1995, p. 1.

(b) where applicable, the non-clinical data and the non-clinical testing methodology followed by the applicant comply with the scientific and technical requirements set out in sections 2.4 and 4 of Part I, in Part IV and, where relevant to non-clinical data, in the Introduction and General Principles of Annex I to Directive 2001/83/EC.

4. Within the period referred to in paragraph 3, the Committee for Advanced Therapies may request the applicant to provide supplementary information within a given time limit.

In that case, the period referred to in paragraph 3 shall be suspended until the supplementary information requested has been provided.

5. When the Committee for Advanced Therapies has completed its evaluation, the Agency shall inform the applicant accordingly and provide him without delay with the following documents:

(a) an evaluation report detailing in particular the reasons for the conclusion reached by the Committee for Advanced Therapies on the application;

(b) if appropriate on the basis of this evaluation, a certificate identifying the quality and, where applicable, non-clinical data submitted and the corresponding testing methodologies followed by the applicant, which meet the scientific and technical requirements referred to in the second subparagraph of paragraph 3;

(c) where deemed appropriate by the Committee for Advanced Therapies, a list of issues for future consideration by the applicant as regards the compliance with the scientific and technical requirements of Annex I to Directive 2001/83/EC of the quality and, where applicable, non-clinical data submitted, and the corresponding testing methodologies followed by the applicant.

*Article 3*

**Site visits**

The Committee for Advanced Therapies may inform the applicant that a site visit of the premises where the advanced therapy medicinal product concerned is being developed is necessary in order to complete its evaluation in accordance with Article 2. It shall inform the applicant of the objectives of the site visit. If the applicant accepts the conduct of a site visit, it shall be carried out by inspectors from the Member States who hold the appropriate qualifications.

In that case, the time-limit laid down in Article 2(3) shall be suspended until the visit report has been made available to the Committee for Advanced Therapies and to the applicant.

*Article 4*

**Combined advanced therapy medicinal products**

1. Where an application for certification relates to combined advanced therapy medicinal products, the additional requirements set out in paragraphs 2 and 3 shall apply.

2. The application for certification of data related to a combined advanced therapy medicinal product may include evidence of conformity with the essential requirements referred to in Article 6 of Regulation (EC) No 1394/2007.

3. The application for certification of data related to 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 data concerning 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. In that case, the period referred to in Article 2(3) shall be suspended until the information requested has been provided.

4. If the application does not include the results of the assessment, the Agency may

(a) 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; or

(b) exclude from the evaluation the check of conformity of the medical device with the essential requirements referred to in Article 6 of Regulation (EC) No 1394/2007.

In the case referred to in point (a), the period referred to in Article 2(3) shall be suspended until the opinion requested has been provided.

In the case referred to in point (b), the evaluation report and any certificate provided shall record the fact that the evaluation excludes the check of conformity of the medical device with the essential requirements. The evaluation report and any certificate provided may also conclude that the interaction and compatibility between the cells or tissues and the medical device cannot be evaluated in the absence of the results of the assessment by a notified body.

*Article 5*

**Scientific guidelines**

In assembling the dossier for application for certification, applicants shall take into account the scientific guidelines published by the Agency relating to the minimum quality and non-clinical data set out in the second and third subparagraphs of Article 2(1) for the certification of advanced therapy medicinal products.

*Article 6*

**Report**

The Agency shall include in the Annual Report of its activities a section on the experience gained as a result of the application of this Regulation. This section shall in particular contain statistical information on the type and number of applications submitted pursuant to this Regulation.

*Article 7*

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

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

Done at Brussels, 24 July 2009.

*For the Commission*
Günter VERHEUGEN
*Vice-President*