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15. When placed on the market, each device must be accompanied by instructions for use giving the following particulars:

— the year of authorization to affix the CE mark,

— the details referred to in 14,1 and 14.2, with the exception of those referred to in the eighth and ninth indents,

— the performances referred to in section 2 and any undesirable side effects,

— information allowing the physician to select a suitable device and the corresponding software and accessories,

— information constituting the instructions for use allowing the physician and, where appropriate, the patient to use the device, its accessories and software correctly, as well as information on the nature, scope and times for operating controls and trials and, where appropriate, maintenance measures,

— information allowing, if appropriate, certain risks in connection with implantation of the device to be avoided,

— information regarding the risks of reciprocal interference [1] in connection with the presence of the device during specific investigations or treatment,

— the necessary instructions in the event of the sterile pack being damaged and, where appropriate, details of appropriate methods of resterilization,

— an indication, if appropriate, that a device can be reused only if it is reconditioned under the responsibility of the manufacturer to comply with the essential requirements.

The instruction leaflet must also include details allowing the physician to brief the patient on the contra-indications and the precautions to be taken. These details should cover in particular:

— information allowing the lifetime of the energy source to be established,

— precautions to be taken should changes occur in the device's performance,

— precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure, acceleration, etc.,

— adequate information regarding the medicinal products which the device in question is designed to administer ,

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— date of issue or the latest revision of the instructions for use.

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16. Confirmation that the device satisfies the requirements in respect of characteristics and performances, as referred to in I. 'General requirements', in normal conditions of use, and the evaluation of the side effects or undesirable effects must be based on clinical data established in accordance with Annex 7.

[1] 'Risks of reciprocal interference' means adverse effects on the device caused by instruments present at the time of investigations or treatment, and vice versa.

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ANNEX 2

EC DECLARATION OF CONFORMITY

(Complete quality assurance system)

1. The manufacturer shall apply the quality system approved for the design, manufacture and final inspection of the products concerned as specified in sections 3 and 4 and shall be subject to EC surveillance as specified in section 5.

2. The declaration of conformity is the procedure by means of which the manufacturer who satisfies the obligations of section 1 ensures and declares that the products concerned meet the provisions of this Directive which apply to them.

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The manufacturer or his authorized representative established within the Community shall affix the CE marking in accordance with Article 12 and shall draw up a written declaration of conformity.

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This declaration shall cover one or more clearly identified devices by means of product name, product code or other unambiguous reference and must be kept by the manufacturer.

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The CE marking shall be accompanied by the identification number of the notified body responsible.

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3. **Quality system**

3.1. The manufacturer shall make an application for evaluation of his quality system to a notified body.

The application shall include:

— all the appropriate items of information for the category of products manufacture of which is envisaged,

— the quality-system documentation,

— an undertaking to fulfil the obligations arising from the quality system as approved,

— an undertaking to maintain the approved quality system in such a way that it remains adequate and efficacious,

— ►M4 an undertaking by the manufacturer to institute and keep updated a post-marketing surveillance system including the provisions referred to in Annex 7. ◄ The undertaking shall include an obligation for the manufacturer to notify the competent authorities of the following incidents immediately on learning of them:

(i) any deterioration in the characteristics or performances, and any inaccuracies in the instruction leaflet for a device which might lead to or have led to the death of a patient or a deterioration in his state of health;

(ii) any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.

3.2. The application of the quality system must ensure that the products conform to the provisions of this Directive which apply to them at every stage, from design to final controls.

All the elements, requirements and provisions adopted by the manufacturer for his quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures. This quality-system documentation must make possible a uniform interpretation of the quality policies and procedures such as quality programmes, quality plans, quality manuals and quality records. ►M4 It shall include in particular the corresponding documentation, data and records arising from the procedures referred to in point (c). ◄

It shall include in particular an adequate description of:

(a) the manufacturer's quality objectives;

(b) the organization of the business and in particular:

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— the organizational structures, the responsibilities of the managerial staff and their organizational authority where quality of design and manufacture of the products is concerned,

— the methods of monitoring the efficient operation of the quality system and in particular its ability to achieve the desired quality of the design and of the products, including control of products which do not conform ,

▼M4

— where the design, manufacture and/or final inspection and testing of the products, or elements thereof, is carried out by a third party, the methods of monitoring the efficient operation of the quality system and in particular the type and extent of control applied to the third party;

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(c) the procedures for monitoring and verifying the design of the products and in particular:

— the design specifications, including the standards which will be applied and a description of the solutions adopted to fulfil the essential requirements which apply to the products when the standards referred to in Article 5 are not applied in full,

— the techniques of control and verification of the design, the processes and systematic actions which will be used when the products are being designed ,

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— a statement indicating whether or not the device incorporates, as an integral part, a substance or a human blood derivative referred to in Section 10 of Annex 1 and the data on the tests conducted in this connection required to assess the safety, quality and usefulness of that substance or human blood derivative, taking account of the intended purpose of the device,

— the pre-clinical evaluation,

— the clinical evaluation referred to in Annex 7;

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(d) the techniques of control and of quality assurance at the manufacturing stage and in particular:

— the processes and procedures which will be used, particularly as regards sterilization, purchasing and the relevant documents,

— product-identification procedures drawn up and kept up to date from drawings, specifications or other relevant documents at every stage of manufacture;

(e) the appropriate tests and trials which will be effected before, during and after production, the frequency with which they will take place, and the test equipment used.

3.3. Without prejudice to Article 13 of this Directive, the notified body shall effect an audit of the quality system to determine whether it meets the requirements referred to in 3.2. It shall presume conformity with these requirements for the quality systems which use the corresponding harmonized standards.

The team entrusted with the evaluation shall include at least one member who has already had experience of evaluations of the technology concerned. ►M4 The evaluation procedure shall include an inspection on the manufacturer's premises and, in duly substantiated cases, on the premises of the manufacturer's suppliers and/or subcontractors to inspect the manufacturing processes. ◄

The decision shall be notified to the manufacturer after the final inspection. It shall contain the conclusions of the control and a reasoned evaluation.

3.4. The manufacturer shall inform the notified body which has approved the quality system of any plan to alter the quality system.

The notified body shall evaluate the proposed modifications and shall verify whether the quality system so modified would meet the requirements referred to in 3.2; it shall notify the manufacturer of its

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decision. This decision shall contain the conclusions of the control and a reasoned evaluation.

4. **Examination of the design of the product**

4.1. In addition to the obligations incumbent on him under section 3, the manufacturer shall make an application for examination of the design dossier relating to the product which he plans to manufacture and which falls into the category referred to in 3.1.

4.2. ►M4 The application shall describe the design, manufacture and performances of the product in question, and it must include the documents needed to assess whether the product conforms to the requirements of this Directive, and in particular Annex 2, Section 3.2, third paragraph, points (c) and (d). ◄

It shall include *inter alia*:

— the design specifications, including the standards which have been applied,

— the necessary proof of their appropriations, in particular where the standards referred to in Article 5 have not been applied in full. This proof must include the results of the appropriate tests carried out by the manufacturer or carried out under his responsibility,

— a statement as to whether or not the device incorporates, as an integral part, a substance as referred to in section 10 of Annex 1, whose action in combination with the device may result in its bioavailability, together with data on the relevant trials conducted,

— the clinical ►M4 evaluation ◄ referred to in Annex 7,

— the draft instruction leaflet.

4.3. The notified body shall examine the application and, where the product complies with the relevant provisions of this Directive, shall issue the applicant with an EC design examination certificate. The notified body may require the application to be supplemented by further tests or proof so that compliance with the requirements of the Directive may be evaluated. The certificate shall contain the conclusions of the examination, the conditions of its validity, the data needed for identification of the approved design and, where appropriate, a description of the intended use of the product.

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In the case of devices referred to in Annex 1, Section 10, second paragraph, the notified body shall, as regards the aspects referred to in that section, consult one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC or the EMEA before taking a decision. The opinion of the competent national authority or the EMEA shall be drawn up within 210 days after receipt of valid documentation. The scientific opinion of the competent national authority or the EMEA must be included in the documentation concerning the device. The notified body will give due consideration to the views expressed in this consultation when making its decision. It will convey its final decision to the competent body concerned.

In the case of devices referred to in Annex 1, Section 10, third paragraph, the scientific opinion of the EMEA must be included in the documentation concerning the device. The opinion shall be drawn up within 210 days after receipt of valid documentation. The notified body will give due consideration to the opinion of the EMEA when making its decision. The notified body may not deliver the certificate if the EMEA's scientific opinion is unfavourable. It will convey its final decision to the EMEA.

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4.4. The applicant shall inform the notified body which issued the EC design examination certificate of any modification made to the approved design. Modifications made to the approved design must obtain supplementary approval from the notified body which issued the EC design examination certificate where such modifications may affect conformity with the essential requirements of this Directive or the conditions prescribed for the use of the product. This supplementary approval shall be given in the form of an addendum to the EC design examination certificate.

5. **Surveillance**

5.1. The aim of surveillance is to ensure that the manufacturer duly fulfils the obligations arising from the approved quality system.

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5.2. The manufacturer shall authorize the notified body to carry out all necessary inspections and shall supply it with all appropriate information, in particular:

— the quality-system documentation,

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— the data stipulated in the part of the quality system relating to design, such as the results of analyses, calculations, tests, pre-clinical and clinical evaluation, post-market clinical follow-up plan and the results of the post-market clinical follow-up, if applicable, etc.,

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— the data stipulated in the part of the quality system relating to manufacture, such as reports concerning inspections, tests, standardizations/calibrations and the qualifications of the staff concerned, etc.

5.3. The notified body shall periodically carry out appropriate inspections and evaluations in order to ascertain that the manufacturer is applying the approved quality system, and shall supply the manufacturer with an evaluation report.

5.4. In addition, the notified body may make unannounced visits to the manufacturer, and shall supply him with an inspection report.

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6. **Administrative provisions**

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6.1. For at least 15 years from the last date of manufacture of the product, the manufacturer or his authorised representative shall keep available for the national authorities:

— the declaration of conformity,

— the documentation referred to in the second indent of Section 3.1, and in particular the documentation, data and records referred to in the second paragraph of Section 3.2,

— the amendments referred to in Section 3.4,

— the documentation referred to in Section 4.2,

— the decisions and reports of the notified body referred to in Sections 3.4, 4.3, 5.3 and 5.4.

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6.2. On request, the notified body shall make available to the other notified bodies and the competent authority all relevant information on approvals of quality systems issued, refused or withdrawn.

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7. Application to the devices referred to in Article 1(4a):

Upon completing the manufacture of each batch of devices referred to in Article 1(4a), the manufacturer shall inform the notified body of the release of the batch of devices and send to it the official certificate concerning the release of the batch of human blood derivative used in the device, issued by a State laboratory or a laboratory designated for that purpose by a Member State in accordance with Article 114(2) of Directive 2001/83/EC.

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ANNEX 3

EC TYPE-EXAMINATION

1. EC type-examination is the procedure whereby a notified body observes and certifies that a representative sample of the production envisaged satisfies the relevant provisions of this Directive.

2. The application for EC type-examination shall be made by the manufacturer, or by his authorized representative established in the Community, to a notified body.

The application shall include:

— the name and address of the manufacturer and the name and address of the authorized representative if the application is made by the latter,

— a written declaration specifying that an application has not been made to any other notified body,

— the documentation described in section 3 needed to allow an evaluation to be made of the conformity of a representative sample of the production in question, hereinafter referred to as 'type', with the requirements of this Directive.

The applicant shall make a 'type' available to the notified body. The notified body may request other samples as necessary.

3. The documentation must make it possible to understand the design, the manufacture and the performances of the product. The documentation shall contain the following items in particular:

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— a general description of the type, including any variants planned, and its intended use(s),

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— design drawings, methods of manufacture envisaged, in particular as regards sterilization, and diagrams of parts, sub-assemblies, circuits, etc.,

— the descriptions and explanations necessary for the understanding of the abovementioned drawings and diagrams and of the operation of the product,

— a list of the standards referred to in Article 5, applied in full or in part, and a description of the solutions adopted to satisfy the essential requirements where the standards referred to in Article 5 have not been applied,

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— the results of design calculations, risk analysis, investigations and technical tests carried out, etc.,

— a declaration stating whether or not the device incorporates, as an integral part, a substance or a human blood derivative as referred to in Section 10 of Annex 1 and the data on the tests conducted in this connection required to assess the safety, quality and usefulness of that substance or human blood derivative, taking account of the intended purpose of the device,

— the pre-clinical evaluation,

— the clinical evaluation referred to in Annex 7,

— the draft instruction leaflet.

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4. The notified body shall:

4.1. examine and evaluate the documentation, verify that the type has been manufactured in accordance with that documentation; it shall also record the items which have been designed in accordance with the applicable provisions of the standards referred to in Article 5, as well as the items for which the design is not based on the relevant provisions of the said standards;

4.2. carry out or have carried out the appropriate inspections and the tests necessary to verify whether the solutions adopted by the manufacturer satisfy the essential requirements of this Directive where the standards referred to in Article 5 have not been applied;

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4.3. carry out or have carried out the appropriate inspections and the tests necessary to verify whether, where the manufacturer has chosen to apply the relevant standards, these have actually been applied;

4.4. agree with the applicant on the place where the necessary inspections and tests will be carried out.

5. Where the type meets the provisions of this Directive, the notified body shall issue an EC type-examination certificate to the applicant. The certificate shall contain the name and address of the manufacturer, the conclusions of the control, the conditions under which the certificate is valid and the information necessary for identification of the type approved.

The significant parts of the documentation shall be attached to the certificate and a copy shall be kept by the notified body.

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In the case of devices referred to in Annex 1, Section 10, second paragraph, the notified body shall, as regards the aspects referred to in that section, consult one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC or the EMEA before taking a decision. The opinion of the competent national authority or the EMEA shall be drawn up within 210 days after receipt of valid documentation. The scientific opinion of the competent national authority or the EMEA must be included in the documentation concerning the device. The notified body will give due consideration to the views expressed in this consultation when making its decision. It will convey its final decision to the competent body concerned.

In the case of devices referred to in Annex 1, Section 10, third paragraph, the scientific opinion of the EMEA must be included in the documentation concerning the device. The opinion shall be drawn up within 210 days after receipt of valid documentation. The notified body will give due consideration to the opinion of the EMEA when making its decision. The notified body may not deliver the certificate if the EMEA's scientific opinion is unfavourable. It will convey its final decision to the EMEA.

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6. The applicant shall inform the notified body which issued the EC type-examination certificate of any modification made to the approved product.

Modifications to the approved product must receive further approval from the notified body which issued the EC type-examination certificate where such modifications may affect conformity with the essential requirements or with the conditions of use specified for the product. This new approval shall be issued, where appropriate, in the form of a supplement to the initial EC type-examination certificate.

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7. **Administrative provisions**

7.1. On request, each notified body shall make available to the other notified bodies and the competent authority, all relevant information on EC type-examination certificates and addenda issued, refused or withdrawn.

7.2. Other notified bodies may obtain a copy of the EC type-examination certificates and/or the addenda to them. The annexes to the certificates shall be made available to the other notified bodies when a reasoned application is made and after the manufacturer has been informed.

7.3. The manufacturer or his authorized representative shall keep with the technical documentation a copy of the EC type-examination certificates and the supplements to them for a period of at least ▶M4 15 years from the manufacture of the last product ◀.

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ANNEX 4

EC VERIFICATION

1. EC verification is the procedure whereby the manufacturer or his authorized representative established within the Community ensures and declares that the products subject to the provisions of section 3 are in conformity with the type as described in the EC type-examination certification and satisfy the requirements of this Directive that apply to them.

2. The manufacturer or his authorized representative established within the Community shall take all measures necessary in order that the manufacturing process ensures conformity of the products to the type as described in the EC type-examination certification and to the requirements of this Directive that apply to them. The manufacturer or his authorized representative established within the Community shall affix the CE marking to each product and draw up a written declaration of conformity.

3. The manufacturer shall, before the start of manufacture, prepare documents defining the manufacturing processes, in particular as regards sterilization, together with all the routine, pre-established provisions to be implemented to ensure uniformity of production and conformity of the products with the type as described in the EC type-examination certificate as well as with the relevant requirements of this Directive.

4. The manufacturer shall undertake to institute and keep updated a ►M4 post-marketing surveillance system including the provisions referred to in Annex 7 ◄. This undertaking shall include the obligation on the part of the manufacturer to notify the competent authorities of the following events immediately on learning of them:

   (i) any change in the characteristics or performances and any inaccuracies in the instruction leaflet for a device which might lead to or have led to the death of a patient or deterioration in his state of health;

   (ii) any technical or medical reason resulting in the withdrawal of a device from the market by a manufacturer.

5. The notified body shall carry out the appropriate examinations and tests in order to check the conformity of the product to the requirements of this Directive by examination and testing of products on a statistical basis, as specified in section 6. The manufacturer must authorize the notified body to evaluate the efficiency of the measures taken pursuant to section 3, by audit where appropriate.

6. **Statistical verification**

6.1. Manufacturers shall present the products manufactured in the form of uniform batches and shall take all necessary measures in order that the manufacturing process ensures the uniformity of each batch produced.

6.2. A random sample shall be taken from each batch. Products in a sample shall be individually examined and appropriate tests, as set out in the standard(s) referred to in Article 5, or equivalent tests shall be carried out to verify their conformity to the type as described in the EC type-examination certificate and thereby determine whether a batch is to be accepted or rejected.

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6.3. Statistical control of products will be based on attributes and/or variables, entailing sampling schemes with operational characteristics which ensure a high level of safety and performance according to the state of the art. The sampling schemes will be established by the harmonised standards referred to in Article 5, taking account of the specific nature of the product categories in question.

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6.4. Where batches are accepted, the notified body shall affix, or cause to be affixed, its identification number to each product and draw up a written certificate of conformity relating to the tests carried out. All products in the batch may be placed on the market except for those products from the sample which were found not to be in conformity.

Where a batch is rejected, the notified body shall take appropriate measures to prevent the placing on the market of that batch. In the

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event of frequent rejection of batches the notified body may suspend the statistical verification.

The manufacturer may, under the responsibility of the notified body, affix the latter's identification number during the manufacturing process.

6.5. The manufacturer or his authorized representative shall ensure that he is able to supply the notified body's certificates of conformity on request.

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7. Application to the devices referred to in Article 1(4a):

Upon completing the manufacture of each batch of devices referred to in Article 1(4a), the manufacturer shall inform the notified body of the release of the batch of devices and send to it the official certificate concerning the release of the batch of human blood derivative used in the device, issued by a State laboratory or a laboratory designated for that purpose by a Member State in accordance with Article 114(2) of Directive 2001/83/EC.

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ANNEX 5

EC DECLARATION OF CONFORMITY TO TYPE

(Assurance of production quality)

1. The manufacturer shall apply the quality system approved for the manufacture and shall conduct the final inspection of the products concerned as specified in 3; he shall be subject to the surveillance referred to in section 4.

2. This declaration of conformity is the procedural element whereby the manufacturer who satisfies the obligations of section 1 guarantees and declares that the products concerned conform to the type described in the EC type-examination certificate and meet the provisions of the Directive which apply to them.

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The manufacturer or his authorized representative established within the Community shall affix the CE marking in accordance with Article 12 and draw up a written declaration of conformity. This declaration shall cover one or more ►M4 devices manufactured, clearly identified by means of product name, product code or other unambiguous reference and must be kept by the manufacturer ◄. The CE marking shall be accompanied by the identification number of the notified body responsible.

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3. **Quality system**

3.1. The manufacturer shall make an application for evaluation of his quality system to a notified body.

The application shall include:

— all appropriate information concerning the products which it is intended to manufacture,

— the quality-system documentation,

— an undertaking to fulfil the obligations arising from the quality system as approved,

— an undertaking to maintain the approved quality system in such a way that it remains adequate and efficacious,

— where appropriate, the technical documentation relating to the approved type and a copy of the EC type-examination certificate,

— an undertaking by the manufacturer to institute and keep up-dated a ►M4 post-marketing surveillance system including the provisions referred to in Annex 7 ◄. The undertaking shall include an obligation for the manufacturer to notify the competent authorities of the following incidents immediately on learning of them:

(i) any deterioration in the characteristics or performances, and any inaccuracies in the instruction leaflet for a device which might lead to or have led to the death of a patient or a deterioration in his state of health;

(ii) any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.

3.2. Application of the quality system must ensure that the products conform to the type described in the EC type-examination certificate.

All the elements, requirements and provisions adopted by the manufacturer for his quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures. This quality-system documentation must make possible a uniform interpretation of the quality policies and procedures such as quality programmes, quality plans, quality manuals and quality records.

It shall include in particular an adequate description of:

(a) the manufacturer's quality objectives;

(b) the organization of the business and in particular:

— the organizational structures, the responsibilities of the managerial staff and their organizational authority where manufacture of the products is concerned,

▼B

— the methods of monitoring the efficient operation of the quality system and in particular its ability to achieve the desired quality ►C1 ——————— ◄ of the products, including control of products which do not conform ,

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— where the manufacture and/or final inspection and testing of the products, or elements thereof, are carried out by a third party, the methods of monitoring the efficient operation of the quality system and in particular the type and extent of control applied to the third party;

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(c) the techniques of control and of quality assurance at the manufacturing stage and in particular:

— the processes and procedures which will be used, particularly as regards sterilization, purchasing and the relevant documents,

— product identification procedures drawn up and kept up-to-date from drawings, specifications or other relevant documents at every stage of manufacture;

(d) the appropriate tests and trials which will be effected before, during and after production, the frequency with which they will take place, and the test equipment used.

3.3. Without prejudice to Article 13, the notified body shall effect an audit of the quality system to determine whether it meets the requirements referred to in 3.2. It shall presume conformity with these requirements for the quality systems which use the corresponding harmonized standards.

The team entrusted with the evaluation shall include at least one member who has already had experience of evaluations of the technology concerned. The evaluation procedure shall include an inspection on the manufacturer's premises.

The decision shall be notified to the manufacturer after the final inspection. It shall contain the conclusions of the control and a reasoned evaluation.

3.4. The manufacturer shall inform the notified body which has approved the quality system of any plan to alter that system.

The notified body shall evaluate the proposed modifications and shall verify whether the quality system so modified would meet the requirements referred to in 3.2; it shall notify the manufacturer of its decision. This decision shall contain the conclusions of the control and a reasoned evaluation.

4. **Surveillance**

4.1. The aim of surveillance is to ensure that the manufacturer duly fulfils the obligations which arise from the approved quality system.

4.2. The manufacturer shall authorize the notified body to carry out all necessary inspections and shall supply it with all appropriate information, in particular:

— the quality-system documentation,

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— the technical documentation,

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— the data stipulated in the part of the quality system relating to manufacture, such as reports concerning inspections, tests, standardizations/calibrations and the qualifications of the staff concerned, etc.

4.3. The notified body shall periodically carry out appropriate inspections and evaluations in order to ascertain that the manufacturer is applying the approved quality system, and shall supply the manufacturer with an evaluation report.

4.4. In addition, the notified body may make unannounced visits to the manufacturer, and shall supply him with an inspection report.

5. The notified body shall communicate to the other notified bodies all relevant information concerning approvals of quality systems issued, refused or withdrawn.

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6. Application to the devices referred to in Article 1(4a):

Upon completing the manufacture of each batch of devices referred to in Article 1(4a), the manufacturer shall inform the notified body of the release of the batch of devices and send to it the official certificate concerning the release of the batch of human blood derivative used in the device, issued by a State laboratory or a laboratory designated for that purpose by a Member State in accordance with Article 114(2) of Directive 2001/83/EC.

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ANNEX 6

STATEMENT CONCERNING DEVICES INTENDED FOR SPECIAL PURPOSES

1. The manufacturer or his authorized representative established within the Community shall draw up for custom-made devices or for devices intended for clinical investigations the statement comprising the elements stipulated in section 2.

2. The statement shall comprise the following information:

2.1. For custom-made devices:

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— the name and address of the manufacturer,

— the information necessary for the identification of the product in question,

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— a statement affirming that the device is intended for exclusive use by a particular patient, together with his name,

— the name of the ►M4 duly qualified medical practitioner ◄ who drew up the prescription and, if applicable, the name of the clinic concerned,

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— the specific characteristics of the product revealed by the prescription,

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— a statement affirming that the device complies with the essential requirements given in Annex 1 and, where applicable, indicating which essential requirements have not been wholly met, together with the grounds.

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2.2. For devices intended for clinical investigations covered in Annex 7:

— data allowing the devices in question to be identified,

— the clinical investigation plan,

— the investigator's brochure,

— the confirmation of insurance of subjects,

— the documents used to obtain informed consent,

— a statement indicating whether or not the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 10 of Annex 1,

— the opinion of the ethics committee concerned and details of the aspects covered by its opinion,

— the name of the duly qualified medical practitioner or other authorised person and of the institution responsible for the investigations,

— the place, date of commencement and duration scheduled for the investigations,

— a statement affirming that the device in question complies with the essential requirements apart from the aspects constituting the object of the investigations and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient.

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3. The manufacturer shall undertake to keep available for the competent national authorities:

3.1. ►M4 For custom-made devices, documentation, indicating manufacturing site(s) and enabling the design, manufacture and performances of the product, including the expected performances, to be understood, so as to allow conformity with the requirements of this Directive to be assessed. ◄

The manufacturer shall take all necessary measures to see that the manufacturing process ensures that the products manufactured conform to the documentation referred to in the first paragraph.

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3.2. For devices intended for clinical investigations, the documentation shall also contain:

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— a general description of the product and its intended use,

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— design drawings, manufacturing methods, in particular as regards sterilization, and diagrams of parts, sub-assemblies, circuits, etc.,

— the descriptions and explanations necessary for the understanding of the said drawings and diagrams and of the operation of the product,

— ►M4 the results of the risk analysis and a list of the standards ◄ laid down in Article 5, applied in full or in part, and a description of the solutions adopted to satisfy the essential requirements of the Directive where the standards in Article 5 have not been applied,

▼M4

— if the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 10 of Annex 1, the data on the tests conducted in this connection which are required to assess the safety, quality and usefulness of that substance, or human blood derivative, taking account of the intended purpose of the device,

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— the results of the design calculations, checks and technical tests carried out, etc.

The manufacturer shall take all necessary measures to see that the manufacturing process ensures that the products manufactured conform to the documentation referred to in 3.1 and in the first paragraph of this section.

The manufacturer may authorize the evaluation, by audit where necessary, of the effectiveness of these measures.

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4. The information included in the declarations covered by this Annex shall be kept for a period of at least 15 years from the date of manufacture of the last product.

5. For custom-made devices, the manufacturer must undertake to review and to document experience gained in the post-production phase, including the provisions referred to in Annex 7, and to implement appropriate means to apply any necessary corrective action. This undertaking must include an obligation for the manufacturer to notify the competent authorities of the following incidents immediately on learning of them and the relevant corrective actions:

(i) any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health;

(ii) any technical or medical reason connected with the characteristics or performance of a device for the reasons referred to in point (i) leading to systematic recall of devices of the same type by the manufacturer.

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ANNEX 7

CLINICAL EVALUATION

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1. **General provisions**

1.1. As a general rule, confirmation of conformity with the requirements concerning the characteristics and performances referred to in Sections 1 and 2 of Annex 1 under the normal conditions of use of the device and the evaluation of the side-effects and of the acceptability of the benefit/risk ratio referred to in Section 5 of Annex 1, must be based on clinical data. The evaluation of this data (hereinafter referred to as clinical evaluation), where appropriate taking account of any relevant harmonised standards, must follow a defined and methodologically sound procedure based on:

1.1.1. Either a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device where:

— there is demonstration of equivalence of the device to the device to which the data relates and,

— the data adequately demonstrate compliance with the relevant essential requirements.

1.1.2. Or a critical evaluation of the results of all the clinical investigations made,

1.1.3. Or a critical evaluation of the combined clinical data provided in 1.1.1 and 1.1.2.

1.2. Clinical investigations shall be performed unless it is duly justified to rely on existing clinical data.

1.3. The clinical evaluation and its outcome shall be documented. This documentation shall be included and/or fully referenced in the technical documentation of the device.

1.4. The clinical evaluation and its documentation must be actively updated with data obtained from the post-market surveillance. Where post-market clinical follow-up as part of the post-market surveillance plan for the device is not deemed necessary, this must be duly justified and documented.

1.5. Where demonstration of conformity with essential requirements based on clinical data is not deemed appropriate, adequate justification for any such exclusion has to be given based on risk management output and under consideration of the specifics of the device/body interaction, the clinical performances intended and the claims of the manufacturer. Adequacy of demonstration of conformity with the essential requirements by performance evaluation, bench testing and pre-clinical evaluation alone has to be duly substantiated.

1.6. All data must remain confidential unless it is deemed essential that they be divulged.

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2. **Clinical investigation**

2.1. *Purpose*

The purpose of clinical investigation is to:

— verify that, under normal conditions of use, the performances of the device comply with those indicated in section 2 of Annex 1,

— determine any undesirable side effects, under normal conditions of use, and assess whether they are acceptable risks having regard to the intended performance of the device.

2.2. *Ethical consideration*

Clinical investigations shall be made in accordance with the Declaration of Helsinki approved by the 18th World Medical Assembly in Helsinki, Finland, in 1964, and amended by the 29th World Medical Assembly in Tokyo, Japan, in 1975 and the 35th World Medical Assembly in Venice, Italy, in 1983. It is mandatory that all measures relating to the protection of human subjects are carried out in the spirit of the Declaration of Helsinki. This includes every step in the clinical investigation from first consideration of need and justification of the study to publication of results.

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2.3. *Methods*

2.3.1. Clinical investigations shall be performed according to an appropriate state of the art plan of investigation defined in such a way as to confirm or refute the manufacturer's claims for the device; the investigations shall include an adequate number of observations to guarantee the scientific validity of the conclusions.

2.3.2. The procedures utilized to perform the investigations shall be appropriate to the device under examination.

2.3.3. Clinical investigations shall be performed in circumstances equivalent to those which would be found in normal conditions of use of the device.

2.3.4. All appropriate features, including those involving the safety and performances of the device, and its effects on the patients, shall be examined.

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2.3.5. All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed.

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2.3.6. The investigations shall be performed under the responsibility of an ►M4 duly qualified medical practitioner or authorised person ◄, in an appropriate environment.

The medical specialist shall have access to the technical data regarding the device.

2.3.7. The written report, signed by the responsible medical specialist, shall comprise a critical evaluation of all the data collected during the clinical investigation.

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ANNEX 8

MINIMUM CRITERIA TO BE MET WHEN DESIGNATING INSPECTION BODIES TO BE NOTIFIED

1. The body, its director and the staff responsible for carrying out the evaluation and verification operations shall not be the designer, manufacturer, supplier or installer of devices which they control, nor the authorized representative of any of those parties. They may not become directly involved in the design, construction, marketing or maintenance of the devices, nor represent the parties engaged in these activities. This does not preclude the possibility of exchanges of technical information between the manufacturer and the body.

2. The body and its staff must carry out the evaluation and verification operations with the highest degree of professional integrity and technical competence and must be free from all pressures and inducements, particularly financial, which might influence their judgement or the results of the inspection, especially from persons or groups of persons with an interest in the results of verifications.

3. The body must be able to carry out all the tasks in one of Annexes 2 to 5 assigned to such a body and for which it has been notified, whether those tasks are carried out by the body itself or under its responsibility. In particular, it must have at its disposal the necessary staff and possess the necessary facilities to enable it to perform properly the technical and administrative tasks connected with evaluation and verification; it must also have access to the equipment necessary for the verifications required.

4. The staff responsible for control operations must have:

   — sound vocational training covering all the evaluation and verification operations for which the body has been designated,

   — satisfactory knowledge of the requirements of the controls they carry out and adequate experience of such operations,

   — the ability required to draw up the certificates, records and reports to demonstrate that the controls have been carried out.

5. The impartiality of inspection staff must be guaranteed. Their remuneration must not depend on the number of controls carried out, nor on the results of such controls.

6. The body must take out liability insurance unless liability is assumed by the State in accordance with national law, or the Member State itself is directly responsible for controls.

7. The staff of the body are bound to observe professional secrecy with regard to all information gained in carrying out their tasks (except *vis-à-vis* the competent administrative authorities of the State in which their activities are carried out) under this Directive or any provision of national law giving effect to it.

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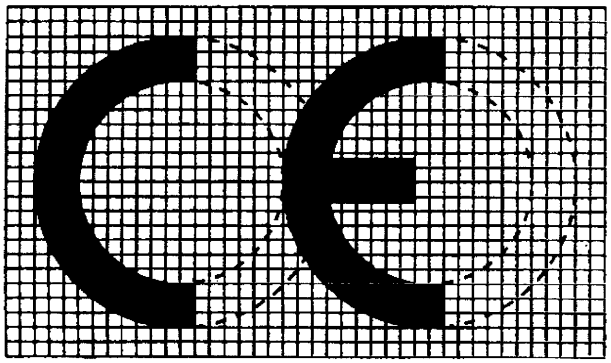
ANNEX 9

CE CONFORMITY MARKING

— The CE conformity marking shall consist of the initials 'CE' taking the following form:



— If the CE marking is reduced or enlarged the proportions given in the above graduated drawing must be respected.

— The various components of the CE marking must have substantially the same vertical dimension, which may not be less than 5 mm.

This minimum dimension may be waived for small-scale devices.

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.