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Consumer goods
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IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION

Regulation (EC) No 1394/2007

PUBLIC CONSULTATION PAPER

DRAFT DETAILED GUIDELINE ON GOOD CLINICAL PRACTICE SPECIFIC TO ADVANCED THERAPY MEDICINAL PRODUCTS

Version: 2 July 2008

Deadline for Public Consultation: 15 October 2008

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

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1. ABOUT THE CONSULTATION

1.1. What is the purpose of this consultation?

Regulation (EC) No 1394/2007 on advanced therapy medicinal products[1] ("the Regulation") lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products (gene therapy, somatic cell therapy and tissue engineering). This Regulation will apply from 30 December 2008.

The European Commission has published on 13 December 2007 an implementation plan, outlining its priorities for the implementation of the Regulation[2]. The implementation plan has been developed and agreed with the European Medicines Agency (EMEA).

As part of this plan, Article 4 of the Regulation requires that detailed guidelines on good clinical practice (GCP) specific to advanced therapy medicinal products be drawn up. This public consultation document presents preliminary proposals to draft such guidance.

1.2. Who is consulted?

Comments on this document are invited from all stakeholders dealing with advanced therapy medicinal products. Stakeholders who are not established within the European Union are equally invited to comment. Comments from Small and Medium-sized Enterprises (SMEs) involved in the sector are especially welcomed.

1.3. How can I contribute?

Contributions should be sent by e-mail to entr-pharmaceuticals@ec.europa.eu, **before 15 October 2008**. An acknowledgement of receipt will be issued for each contribution received, within five working days except in August. Contributions will be made publicly available on the 'Pharmaceuticals' website of the Commission once the consultation period is over, unless a specific request for confidentiality is made, in which case only an indication of the contributor will be disclosed. If you do not wish your contribution to be made public, please clearly indicate so.

1.4. What will happen next?

All contributions will be carefully analysed. A summary of the outcome of the consultation will be published on the 'Pharmaceuticals' website of the European Commission and also sent directly to all contributors. Any future proposal on GCP guidance specific to advanced therapy medicinal products will build on this consultation.

1.5. Any questions?

Please contact the European Commission:
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[1] OJ L324, 10.12.2007, p. 121.

[2] http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm

2. DRAFT GUIDELINE ON GCP SPECIFIC TO ADVANCED THERAPY MEDICINAL PRODUCTS

2.1. Introduction and scope

This draft guideline is intended to set out GCP aspects specific to advanced therapy medicinal products (ATMPs), in an area of limited experience and rapid evolution. It focuses on GCP requirements for advanced therapy investigational medicinal products (ATIMPs) which are new or different to those for other investigational medicinal products. It does not replace but supplements the principles and detailed guidelines set out in Directive 2005/28/EC[3], Volume 10 of the Rules Governing Medicinal Products in the European Union[4], including in particular the Note for guidance on Good Clinical Practice[5]. This guideline should be read in conjunction with these reference documents. Attention should also be paid to other guidelines specific to advanced therapies[6].

Where an ATIMP contains or consists of tissues or cells, other actors than the sponsor and the investigator need to be considered: this includes tissue/blood establishments, procurement organisations, animal facilities and donors. It is important to put the role of these actors, and their applicable legislation, in the context of the roles and responsibilities for clinical trials.

2.2. Overarching GCP principles

1. The use of each ATIMP should be traceable. The individual product should be traceable through the sourcing, manufacturing, packaging, storing, transport, delivery to the hospital/institution/private practice, administration to the subjects, reconciliation and destruction or final disposition. The system should contain sufficient detail to allow linking of each individual product to the individual subject who received the product and back to the donor, if the product or part of it originates from a donor, and vice versa.

2. Subjects should be followed-up during and after the completion of the clinical trial both for their own care and to allow data collection as needed. Processes should be established to enable contact with subjects to be maintained throughout the required follow up period. The subjects should be provided with information on the treatment given and contact points (e.g. subject card, see section 2.4.2).

3. The donation, procurement and testing of human cells and tissues used for the manufacturing of an ATIMP should be carried out in accordance with the human cells/tissue and blood Directives[7] by establishments which are qualified, accredited, designated, authorised or licensed by the relevant competent authority for the purpose of those activities.

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

[4] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm

[5] CPMP/ICH/135/95

[6] http://www.emea.europa.eu/htms/human/mes/advancedtherapies.htm

[7] Directive 2004/23/EC (OJ L 102, 7.4.2004, p. 48) and Directive 2002/98/EC (OJ L 33, 8/2/2003 p. 30), and their related implementing Directives.

4. Where tissues or cells of animal origin are used in the manufacture of an ATIMP, the sourcing procurement and testing should be done in accordance with the 'Points to consider on xenogenic cell therapy medicinal products'[8].

2.3. Traceability

2.3.1. General requirements

Good clinical practice imply requirements for accountability of investigational medicinal products (IMPs). These requirements contribute significantly to the traceability of an IMP from the point of release of the IMP from the manufacturer onwards. The requirements for traceability may be achieved by ensuring that the systems established for traceability and for IMP accountability are integrated so that the special requirements of each are addressed.

Where an ATIMP contains human cells or tissues, the sponsor of the trial, as well as the investigator or institution where the product is used, should ensure that the traceability systems are complementary to, and compatible with, the requirements laid down in the human cells/tissues or blood Directives. Where the tissues or cells are of animal origin the requirements for traceability are also applicable and should ensure there is a clear documented link from the donor animal to the human clinical trial subject and vice versa.

In the event that the clinical trial is suspended or prematurely ended, the sponsor and investigator/institution should continue the maintenance of the traceability system.

The guideline on traceability referred to in Article 15(7) of the Regulation should also be applicable to clinical trials on ATIMPs.

2.3.2. Responsibilities

2.3.2.1. Responsibility of the sponsor

The sponsor of a clinical trial with an ATIMP should ensure that a traceability system is established and maintained. The system should 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 investigator/institution where the product is used, application of the product to the study subject or other final reconciliation and disposal or destruction of the product.

Where multiple parties are involved the sponsor should ensure that the role of each is clear (*e.g.* where the tissue or cells are obtained from an autologous donor by a surgeon at the same site as the administration of the ATIMP to the subject by the investigator) and that the integrity of the traceability is maintained.

The sponsor should ensure, through contractual agreements with the tissue or blood establishment, or animal facility sourcing animal tissue or cells, the manufacturer, and the investigator that the traceability of the ATIMP can be linked to the donor, procurement organisation and via the investigator/institution to the study subject, and vice versa.

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[8] CPMP Points to consider on xenogenic cell therapy medicinal products June 2004 (CPMP/1199/02).

2.3.2.2. Responsibility of the tissue/blood establishment /procurement organisations or animal facility

The tissue or blood establishment or procurement organisation or animal facility should be responsible for the traceability with respect to the donation and procurement of the cell or tissue material needed for the manufacturing of the ATIMP, up to the delivery of that material to the manufacturer.

2.3.2.3. Responsibility of the manufacturer of the ATIMP

The manufacturer is responsible for ensuring traceability during the manufacturing process up to the release of the finished ATIMP to the sponsor for use in the clinical trial and its delivery to the clinical trial site, where the latter is also undertaken by the manufacturer or under their control. Where the sponsor takes care of the delivery of the ATIMP from the manufacturer to the clinical trial site the sponsor is responsible for ensuring the traceability.

2.3.2.4. Responsibility of the investigator/institution

The institution/investigator and/or pharmacist or other individual who is designated by the investigator institution should establish and maintain a system for subject and product traceability. That system should contain sufficient detail to allow linking of each product, delivered to the investigator/institution, to the study subject receiving it and vice versa.

2.3.3. Archiving responsibilities of the sponsor, manufacturer and the investigator/institution for traceability

The sponsor of the trial, the manufacturer, and the investigator or institution where the ATIMP is used, should keep their parts of the traceability records for a minimum of 30 years after the expiry date of the product, or longer if required by the applicable regulatory requirements or by an agreement with the sponsor.

The minimum data set to be kept is that outlined below[9]:

[9] By analogy with Annex VI to Directive 2006/86/EC (OJ L 294, 25.10.2006, p. 32).

BY TISSUE ESTABLISHMENTS/PROCUREMENT ORGANISATION/ANIMAL FACILITY OR BY THE SPONSOR/MANUFACTURER (as applicable depending on the activities undertaken by each)

Donor/source animal identification

Donation identification that will include at least:

- Identification of the procurement organisation, tissue establishment or animal facility
- Unique Donation ID number
- Date of procurement
- Place of procurement
- Type of donation (e.g. single v multi-tissue; autologous v allogenic; living v deceased)
- Type of tissues and cells

Product identification that will include at least:

- Identification of the tissue establishment/animal facility/manufacturer
- Type of tissue and cell/product (basic nomenclature)
- Pool number (if applicable)
- Split number (if applicable)
- Expiry date
- Tissue/cell status (i.e. quarantined, suitable for use etc.)
- Description and origin of the products, processing steps applied materials and additives coming into contact with tissues and cells and having an effect on their quality and/or safety.
- Identification of the facility issuing the final label

BY INVESTIGATOR/INSTITUTION RESPONSIBLE FOR HUMAN APPLICATION

Human application identification that will include at least:

- Identification of the investigator/institution
- Identification of the supplier tissue establishment
- Identification of the clinician or end user/facility
- Type of tissues and cells
- Product identification
- Identification of the recipient
- Date of application
- Date of distribution/disposal

It is the responsibility of the sponsor to inform the investigator/institution as to when these documents do no longer need to be retained.

2.4. Safety reporting and long term follow-up

2.4.1. Notification of Adverse Events and Reactions

The process for notification of adverse events and adverse reactions by the investigator and the sponsor in the context of clinical trials are laid down in articles 16 and 17 of Directive 2001/20/EC. New events related to the conduct of the trial or the development of the ATIMP and likely to affect the safety of the subjects should be reported. This includes:

– a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;

– a significant hazard to the subject population such as lack of efficacy of an investigational medicinal product used for the treatment of a life-threatening disease.

The sponsor should provide information and training to the investigator on any particular requirement for the reporting of adverse events and this reporting process should clearly be outlined in the clinical trial protocol. The following safety issues are of particular concern:

– Adverse events related to the surgical procedure or other aspects of the product application process;

– Suspected or confirmed cases of infection;

– Unexpected reactions (e.g. hypersensitivity, immunological, toxic).

The competent authority of the Member State concerned by a serious adverse reaction occurring in a clinical trial with an ATIMP containing human cells or tissues or a combined ATIMP, should inform the relevant national authorities responsible for implementing the tissue/cell and blood Directives and/or medical device Directives[10].

2.4.2. Long Term Follow-up

The need for and the nature of follow-up and if applicable long-term follow-up, after the end of the trial should be determined by the sponsor for each clinical trial based on the nature of the ATIMP, the current state of knowledge regarding that ATIMP and a risk analysis. The sponsor should also take into account any Community guidance on follow-up of subjects treated with particular types of ATIMPs[11]. The follow-up should be described in the protocol, and amended as needed in accordance with the evolving experience with the ATIMP. The follow-up should be considered from the following aspects:

– follow-up for the protection of the individual subject i.e. clinical follow-up;

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[10] Council Directive 90/385/EEC relating to active implantable medical devices (OJ L 189, 20.7.1990, p.17) and Council Directive 93/42/EEC concerning medical devices (OJ L 169, 12.7.1993, p. 1).

[11] See for example the EMEA guideline on the follow-up of patients treated with gene therapy medicinal products (EMEA/CHMP/GTWP60436/2007- draft)

– follow-up for the purpose of collection of data (which might not involve all subjects) i.e. safety follow-up and efficacy follow-up.

Where follow-up is required the sponsor needs to ensure that there is a process in place for follow-up of the subjects treated with the product even in cases where the product development is discontinued and/or (former) sponsor ceases to exist as a legal entity. This may be achieved, for instance, by:

– appropriate information about follow-up of the subjects after the end of the clinical trial provided to healthcare establishments that served as centres for the particular clinical trial;

– websites/phone-lines that provide data/consultation in case of complications;

– subject alert cards that inform treating physicians about the product used and any independent registries or other sources of data available in case of safety/efficacy issues, and of the need to inform the competent authority in the event of certain serious adverse reactions. These alert cards should contain as minimum the name of the subject, a physician contact number and information regarding the medical treatment received.

Where a subject is withdrawn from a trial at their own request or based on a decision of the investigator the follow-up should be maintained, subject to the consent of the subject.

2.5. GCP and Ethics Committee

The ethics committee should consider the following GCP aspects which should also be addressed in the information, including written information, provided to the subject:

– Subject data protection and confidentiality including arrangements for traceability;

– The irreversible nature of certain ATIMP applications, and the information provided to subjects in that context;

– Any particular arrangements for informed consent by vulnerable subjects (paediatrics, mentally incapacitated);

– Situations where the donor is a relative of the subject to be included in the trial and the protection from “sibling/parent” pressure;

– The arrangements for traceability;

– The definition of the end of the trial;

– The arrangements for long term clinical, safety and efficacy follow up;

– The inconveniences of long term follow up;

– The need for the presence of a representative of the sponsor for assistance in the administration of the ATIMP;

– Risks and precautions related to shedding in the context of ATIMPs involving gene therapy.

2.6. GCP and Investigator/Institution

The following consideration should be taken into account for investigators in the context of clinical trials with ATIMPs:

- The investigator should have knowledge of the requirements for storage, handling, administration, and destruction or disposal of the ATIMP including any hazard to those handling the product and risk to the environment;

- The investigator should have knowledge on the use, application, implementation or administration of the ATIMP and requirements for clinical follow up;

- The investigator should ensure that the particular requirements for the application of the ATIMP, such as standardisation of surgical procedures and training of the healthcare professionals involved, are communicated to the investigator site team including the surgeons or other specialists involved;

- The investigator should have knowledge of the risk analysis of the ATIMP (see section 2.4.2);

- The investigator should establish and maintain a system for subject and product traceability (see section 2.3.2);

- The investigator should keep the traceability clinical trial records for a minimum of 30 years (see section 2.3.3);

- The investigator should be aware of the adverse event and adverse reaction reporting process, including reactions related to application of the ATIMP (see section 2.4.1);

- The investigator should inform the trial subject and where applicable their legal representative of the particular issues that arise for ATIMPs:

    - The need for the presence of a representative of the sponsor for assistance in the administration of the ATIMP;

    - The arrangements for long term clinical, safety and efficacy follow up , including the information (subject card) to be provided to the subject in the event of problems arising after the end of the trial;

    - The inconveniences of long term follow up;

    - Subject data protection and confidentiality especially in relation to arrangements for traceability;

    - The irreversible nature of certain ATIMP applications, and the information provided to subjects in that context;

    - The arrangements for traceability.

2.7. GCP and Sponsor

The following consideration should be taken into account for sponsors in the context of clinical trials with ATIMPs:

- The sponsor should establish and maintain a system for subject and product traceability (see section 2.3.2);

- The sponsor should keep the traceability clinical trial records for a minimum of 30 years (see section 2.3.3);

- The sponsor should implement the appropriate adverse event and adverse reaction reporting process as required by the legislation (see section 2.4.1);

- The sponsor should be responsible to ensure that an ongoing risk analysis based on existing knowledge of the type of product and its intended use is performed and provided to the investigator involved in a clinical trial with that ATIMP (see section 2.4.2);

- The sponsor should identify the need for and the nature of clinical, safety and or efficacy follow-up required (see section 2.4.2);

- The sponsor should establish the particular requirements for the application of the ATIMP, such as standardisation of surgical procedures and training of the investigator involved;

- The sponsor should train the investigator in the requirements for storage, handling, administration, and destruction or disposal of the ATIMP including hazards to those handling the product and risk to the environment;

- The sponsor should train the investigator on the use, application, implantation or administration procedures of those ATIMPS that may require specific concomitant therapy and may involve surgical procedures. Information on the standardisation and optimisation of these procedures during clinical development should be provided. The sponsor should also identify where their personnel need to be involved in these procedures and describe this in the protocol or associated document that is included in the applications to the competent authority and ethics committee and in the agreements with the clinical investigator site;

- The sponsor should notify serious breaches of GCP to competent authorities.

2.8. Protocol

The following considerations should be taken into account by the sponsor in relation to the content of the protocol:

- There are variabilities in the nature of ATIMPs and the diseases for which they are used that need to be foreseen in the protocol design. The protocol should foresee any necessary flexibility that may be required for the handling of this variability inherent in the development of certain ATIMPs, for example:

    - The acceptable range of cell numbers and cell viability;

    - Appropriate windows of acceptability for inclusion and exclusion criteria.

- Where an ATIMP contains human cells or tissues, the protocol should contain detailed information on:

  - The donation, procurement and testing of the cells or tissues and donor type and whether or not these are part of the trial process;

  - The criteria for suitability of the donated material to comply with defined requirements.

- Where an ATIMP incorporates a medical device (i.e. a combined advanced therapy medicinal product), the protocol should contain detailed information on:

  - A description of the characteristics, performance and purpose of the device;

  - Evidence of conformity with essential requirements with the regulations.

- The definition of the end of the trial;

- Instructions to ensure the blinding of the trial where the person involved at the clinical site in the preparation of the ATIMP cannot to be unblinded whilst the person responsible for the administration of the ATIMP needs to be blinded;

- Information on the follow up (including long-term follow-up) strategy expected for the ATIMPs with clear objectives , based on appropriate risk assessment;

- Information on the application of the ATIMPs when this application may require specific concomitant therapy and may involve surgical procedures. This includes information on the standardisation and optimisation of the processes involved including where applicable the surgical procedures;

- Instructions on any local preparation or reconstitution required;

- In case of ATIMPs involving gene therapy, information on shedding and any precautions required should be provided where applicable;

- Information on any particular requirements for safety reporting such as:

  - adverse events related or the surgical procedure or other aspects of the product application process;

  - episodes of infection.

- Specific requirements relating to subjects withdrawn from the trial at their own initiative or that of the investigator, in particular aspects relating to the follow-up strategy;

- Traceability procedures and documentation;

2.9. Investigator Brochure

The following consideration should be taken into account by the sponsor in relation to the content of the Investigator Brochure:

- A description of the scope and sufficiency of existing information and its limitations;

- Information obtained from ongoing risk analysis based on existing knowledge of the type of product and its intended use;

– Information on the risk management plan (for marketed products);

– Information on the risk to the environment;

– Information on the reporting of lack of efficacy;

– Information on the (S)AE SAR reporting expected. Information on the long-term safety issues, such as infections, immunogenicity/immunosuppression and malignant transformation as well as the durability of the associated medical device/biomaterial component;

– Information on product protection (storage, transportation, handling etc.);

– Information on product safety handling, containment etc;

– Information on product disposal;

– A long term update may be appropriate depending on the generation of relevant new information.

2.10. Essential documents

The clinical trial records should be kept until 5 years after the end of the follow-up period or longer if required by other legislation.

The traceability records should be kept for a minimum of 30 years after the expiry date of the product, or longer if required by the applicable regulatory requirements or by an agreement with the sponsor.

2.10.1. Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

Details of the process, responsibilities and documentation required to document the link from the donor to the subject receiving the product and vice versa. Each party should hold the necessary information linking the donor information to the ATIMP and the clinical trial subject and vice versa.

2.10.2. During the Clinical Conduct of the Trial

Each party should hold the necessary information linking the donor information to the ATIMP ad the clinical trial subject and vice versa

– File of the investigator:

  – The link from the manufactured ATIMP delivered to that clinical trial site and from the clinical trial site to the patient code, patient identification and medical file.

– File of the sponsor:

  – The link from the manufactured ATIMP to the clinical trial site and from the clinical trial site to the patient code.

- File of the manufacturer:
    - The link from the donated material to the manufactured ATIMP.
- File of the tissue establishment:
    - The link from donor to the donated material.

2.10.3. After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 2.10.1 and 2.10.2 should be in the file together with the following:

- File of the investigator and sponsor.
    - Follow-up procedures, contact information and data collected, to document the conduct of the clinical follow-up, safety follow-up and efficacy follow-up required.