European Medicines Agency
Inspections

London, 15 Ocrober 2008
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Mr Martin Terberger,
European Commission,
Enterprise Directorate-General,
Avenue d'Auderghem, 45
1040 Bruxelles,
BELGIUM.

Dear Mr Terberger,

Subject: Comments to the draft detailed guideline on Good Clinical Practice specific to advanced therapy medicinal products (Version: 2 July 2008)

EMEA is pleased to provide some comments to the above mentioned guideline published by the Commission for public consultation on 4th July 2008.

Comments have been requested from the CHMP and its concerned Working Parties (BWP, CBPWP, GTWP, EWP) and from the GCP Inspectors Working Group. The comments received are summarised under each section of the guideline below and any amendment suggested highlighted with tracking changes. This summary has been discussed at CHMP as well.

EMEA wants to remind that following a request from the European Commission for advice on the GCP requirements specific to Advanced Therapy Medicinal Products (ATIMPs) EMEA forwarded (6 June 2008) the recommendations of its drafting group on the content of this guideline. EMEA also provided a cover letter highlighting some points that need to be considered either in the context of this detailed guideline or in a possible future revision of Directive 2005/28/EC, or in other guidance such as those on traceability, on GMP, or on use of cells or tissues of animal origin.

We would appreciate if you could keep us informed of progress in the GCP area.

Yours sincerely,

Emer Cooke
Head of Inspections Sector, EMEA

cc. Stefan Fuehring (DG Enterprise), Fergus Sweeney, Ana Rodriguez, David Cockburn, Patrick Celis, Arielle North (EMEA)

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EMEA COMMENTS ON

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

General comments

As highlighted in the letter that EMEA forwarded to the European Commission on 6th June 2008 with the recommendations of its drafting group on the content of this guideline and based on the text of the guideline published now by the Commission for consultation, EMEA believes that it is important to continue the following assumptions:

- the pharmaceutical legislation and specifically the clinical trial Directive 2001/20/EC and its implementing legislation and guidelines take precedence,
- the definitions of ATPs apply also to ATIMPs, without need for any further legislation,
- EMEA has also assumed the following but this may need further clarification e.g. in an amendment to directive 2005/28/EC, as the ATP regulation only seems to clarify this for marketed products:
    - the tissue and cell, and blood directives apply to those activities up to the supply of the tissue/cell/blood material to the manufacturer of the ATIMP, including donation, procurement and testing
    - the safety reporting requirements of Directive 2001/20/EC apply, and not those of the tissue/cell/blood or device directives, but we are unsure if some responsibilities still remain on the competent authority or the sponsor in relation to reporting to the tissue and blood establishments, or in relation to device components

EMEA also continue to believe that some elements of the ATP regulation may well need additional reinforcement in legislation as we understand they currently only apply as obligations in relation to marketed ATPs, for instance:

- Traceability requirements
- Long term follow-up
- Interface with tissue and blood establishments
- The need or not for CE marking of device components in a ATIMP, and the authority to decide that this is not necessary (given to CAT for marketed product)

In addition the application of the device directives and clinical trial directive in the context of a clinical trial of a combined product where it is likely in many cases that both the device and cell or tissue component will be innovative and the device will not therefore be CE marked continue to require clarification. This was also highlighted in the letter sent to the European Commission on 6th June 2008 with our recommendations on the content of this guideline.

Specific comments

The following specific recommendations are made taking into account that the "target audience" of this guideline has a large component of Small and Medium Enterprises (SMEs), non-commercial sponsors/investigators and clinical investigators, who may be unfamiliar with the multiple sets of legislation that apply, and would have difficulty in determining and interpreting the applicable texts at each step of the process:

1- Sections to be added:

1.1 Legal basis

The reference to the legal basis for this document is missing in this guideline and should be included.

1.2 Definitions

A section on definitions should be added. There are many terms used in this guideline like "tissue establishment", "procurement organization" etc. perhaps not very familiar for those reading this guideline. The Commission is asked to reconsider the proposal made for this section in the proposal sent by EMEA to the Commission on 6 June 2009 or alternatively cross references should be made in the guideline to the referenced documents where such definitions can be found.

1.3- Donor

It is recommended that that a "Donor" section should be included in order to bring the attention of those actors involved in the conduct of the clinical trials, and mainly the investigators, to the legislation governing donation and the interactions with/obligations to the donors (e.g. informed consent, compensation, eligibility etc.). It is suggested that only placing a cross-reference in the section about the GCP principles (section 2.2) is insufficient. This is especially relevant for those ATIMPs involving autologous donations or donors who are relatives of the patient and where the investigator/institution procures the cells for the manufacturing of the ATIMPs from the patient/relative (donor) involved in the clinical trial run at that investigator institution. The Commission should reconsider the inclusion of such a section – the following text is proposed:

> "Where an ATIMP contains human cells or tissues, the legal obligations in relation to the donors (consent, eligibility of donors, compensation, data protection and confidentiality) are laid down in Directive 2004/23/EC and its implementing Directive 2006/17/EC as regards human cells and tissues other than blood cells and Directive 2002/98/EC and its implementing Directive 2004/33/EC as regards human blood cells.
>
> Where tissues or cells are sourced from an animal origin for the manufacture of an ATIMP the process of donor animals are covered by the CPMP Points to consider on xenogenic cell therapy medicinal products."

1.4- Procurement organizations, tissue or blood establishment and animal facilities

It would be helpful to the users of the guideline if this section could clarify under which legislation the obligations in relation to the activities of these organizations or establishments fall. A little more detail than that provided under principles would be more useful.

2. Title of the guideline

The term "advanced therapy medicinal products" should be replaced by the term "advanced therapy investigational medicinal product" which is the term used in the context of clinical trials and which covers those products with or without a marketing authorization used in a clinical trial on the basis of a Clinical Trial Authorisation. The legal obligations that relate to a medicinal product are different to those that relate to investigational medicinal products.

3- Section 2.1 Introduction and scope

As in comment 2, replace "advanced therapy medicinal" product by "advanced therapy investigational medicinal product".

4- Section 2.3.3 Archiving responsibilities of the sponsor, manufacturer and the investigator/institution for traceability

EMEA has been made aware that additional information to the documentation to ensure traceability is needed and therefore the following amendments (shown in track changes) are recommended:

"The minimum data set to be kept is that outlined below (as applicable depending on the activities undertaken by each):

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BY TISSUE ESTABLISHMENTS/PROCUREMENT ORGANISATION/ANIMAL FACILITY (by analogy with Annex VI, of the Directive 2006/86/EC[12] implementing the uman tissue and cell Directive 2004/23/EC[5]),

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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/animal ID number
- Date of procurement
- Place of procurement
- Type of donation (e.g. single v multi-tissue; autologous v allogeneic v xenogeneic; living v deceased)
- Type of tissues and cells

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Product identification that will include at least:

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- Identification of the procurement organisation, tissue establishment/animal facility,

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- 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 THE MANUFACTURER

Information on the material received from the Procurement organisation, tissue establishment or animal facility as applicable:

- Identification of the tissue establishment/animal facility/any intermediaries if applicable
- Type of tissue and cell/product (basic nomenclature)
- Pool number (if applicable)
- Split number (if applicable)
- Tissue/cell status (i.e. quarantined, suitable for use etc.)

ATIMP identification that will include at least:

- 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 sponsor, contract research organization or investigator/institution to whom the product is supplied
- Product name/code
- Pharmaceutical form, route of administration, quantity of dosage units and strength
- Batch and/or code number
- Trial reference code
- Trial subject identification number
- Expiry date
- Date of distribution/disposal

Release of the finished product by the Qualified Person

BY THE SPONSOR

According to section 8 of the Note for guidance on Good Clinical Practice[5] the following essential documents should be kept by the sponsor before, during and after the conduct of the trial:
- Shipping Records for IMP (8.2.15, 8.3.8):
- Certificate of analysis of the IMP (8.2.16, 8.3.9)
- Treatment allocation and decoding documentation (8.2.17, 8.4.6
- IMP accountability at the site (8.3.23, 8.4.1), including final disposition of both used and unused product.

These records contain information relevant for traceability purposes and at least the following minimum data set from these records should be kept for 30 years:

- Identification of the manufacturing site
- Identification of the investigator/institution that used the ATIMP
- Product name/code
- Pharmaceutical form, route of administration, quantity of dosage units and strength
- Batch and/or code number
- Trial reference code
- Trial subject code
- Expiry date
- Date of application

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<#>Identification of the facility issuing the final label¶

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BY INVESTIGATOR/INSTITUTION RESPONSIBLE FOR HUMAN APPLICATION

According to section 8 of the Note for guidance on Good Clinical Practice[5] the following essential documents should be kept by the invesrtigator before, during and after the conduct of the trial:
- Shipping Records for IMP (8.2.15, 8.3.8):
- Certificate of analysis of the IMP (8.2.16, 8.3.9)
- Treatment allocation and decoding documentation (8.2.17, 8.4.6
- Subject identification code list (8.3.21, 8.4.3)
- IMP accountability at the site (8.3.23, 8.4.1) including final disposition of both used and unused product.

These records contain relevant information for traceability purposes and at least the following minimum data set from these records should be kept for 30 years:

- Identification of the investigator/institution,
- Identification of the sponsor and contract research organization where applicable,
- Identification of the manufacturing site,
- Product name/code,
- Pharmaceutical form, route of administration, quantity of dosage units and strength,
- Batch and/or code number,
- Trial reference code,
- Trial subject code,
- Subject identification code list (8.3.21, 8.4.3) (links the name of the subject to the trial subject code),
- Expiry date,
- Date of administration,

The subject medical records should also contain the product name/code, the trial reference code, trial subject code and administration dates and dose in order to ensure that a link can be made back to the identity of the product and the further traceability records of the investigator and sponsor.

The investigator site should also retain records of any product that was unused or destroyed and of its final status.

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

5- Section 2.4.1 Notifications of adverse events and reactions

In the 2nd sentence of the first paragraph it should be made clear that the reporting lines for these "New events" must be the same as already regulated and therefore the following text is recommended (see track changes):

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 according to the existing timelines for expedited reporting

6- Section 2.6 GCP and Investigator/Institution

EMEA recommends making some changes for better understanding and consistency in the order of some of the bullet points as follow (see track changes):

- The investigator should establish and maintain a system for subject and product traceability (see section 5.4.2).
- The investigator should keep the traceability clinical trial records for a minimum of 30 years (see section 5.4.3).
- The investigator should be aware of the adverse event and adverse reaction reporting process, including reactions related to application of the ATIMP (see section 5.5.1).
- The investigator should have knowledge of the risk analysis of the ATIMP (see section 5.5.2).
- The investigator should inform the trial subject and where applicable their legal representative of the particular issues that arise for ATIMPs
    - The irreversible nature of certain ATIMP applications, and the information provided to subjects in that context.
    - The need for the presence of a representative of the sponsor for assistance in the administration of the ATIMP.
    - The arrangements for traceability.
    - Subject data protection and confidentiality especially in relation to arrangements for traceability.
    - 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.

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<#>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.¶

7- Section 2.7 GCP and Sponsor

EMEA has just wants to make an editorial change as follow (see track changes):

- The sponsor should identify the need for and the nature of clinical, safety and/or efficacy follow-up required (see section 5.5.2).

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8- Section 2.8 Protocol

In page 12, the fifth and seventh bullet point should read as follow (see track changes):

- Evidence of conformity with essential requirements referred to in article 6 of the advanced therapy regulation.

- Instructions to ensure the blinding of the trial where the person involved at the clinical trial site in the preparation of the ATIMP cannot be blinded whilst the...

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In addition it is recommended to change the order of one bullet point as follow (see track changes):

- 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.
- The definition of the end of the trial.

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9- Section 2.10.2 During the clinical conduct of the trial

EMEA suggests rewording the following sentence as follow (see track changes):

Each party should hold the necessary information to ensure bidirectional traceability, linking the donation information at the procurement site to the ATIMP and the clinical trial subject at the clinical site to the ATIMP, whilst ensuring the data protection legally required for both the donor and the clinical trial subject.

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