EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Cosmetics and Medical Devices

SUBMISSION OF COMMENTS
ON THE DRAFT GUIDELINE ON GOOD CLINICAL PRACTICE SPECIFIC TO ADVANCED THERAPY MEDICINAL PRODUCTS

COMMENTS FROM: Eucomed	**Confidential: Yes [ ] No [X]**

GENERAL COMMENTS

Long Retention Time for Traceability Records:

The retention time for traceability records is 30 years after the expiration date of the product or longer. As this requirement is traceable to Directive 2004/23/EC on standards for quality and safety of human tissues and cells, it probably can't be changed. However, the retention period is quite long. The US requirement for retention of records for human cells, tissues, and cellular and tissue based products is at least 10 years after the date of administration per 21 CFR 1271.270.

Lack of Distinction between Cell and Tissue Products and Gene Therapy Products:
The document frequently mentions cells and tissues but mentions gene therapy products in only a few places. How do the requirements apply to a gene therapy that is not also a somatic cell therapy? How does this guideline relate to the EMEA guideline entitled “Notes for Guidance on the Quality, Pre-clinical and Clinical aspects of gene transfer medicinal products” (CPMP/BWP/3088/99, issued 24 april 2001)

Document Continuity:
In general, we found the document difficult to follow. Requirements like sponsor, manufacturer, investigator/institution responsibilities and notification of adverse events and reactions appear in several places in the document. However, the sections are not well linked and consistent. Specific examples follow.
--On page 12, the protocol requirements for safety reporting should be linked to and consistent with section 2.4.1.
--On page 13, the investigator brochure requirements for SAE (SAR) reporting should be linked to and consistent with section 2.4.1.
--Sections 2.10.1 and 2.10.2 should link back to section 2.3.2 on responsibilities.

I miss paragraphs on the necessity of
the involvement of the Ethics Committee for the use of Advanced therapies also in post-market studies, and
the implementation of an Informed Consent process for all patients in use of Advanced therapies. Today, this is practiced on donors and recipients, even in routine use of hematopoietic stem cell therapy (covering SC collection and transplantation).
The specific overarching GCP and the Regulation for Advanced Therapies should be formulated such that they guarantee the freedom of patients to choose or to decline the use of Advanced therapies on them, and that they assure

a) the involvement of the local (hospital) EC even if the products of the AT are created in the same clinical center as they are used
b) the traceability of all products of AT independent of their involvement in a clinical investigation for development of AT, or in a post-market trials or in routine use (as part of standard of care).

Commission européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel - Belgium. Telephone: (32-2) 299 11 11.
Telephone: direct line (32-2) 296 81 58. Fax: (32-2) 296 64 67.

E-mail: ENTR-COSM-MED-DEV@ec.europa.eu

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Page, Section, Line n°	**Comment and Rationale**	**Proposed change (if applicable)**
2.2. Overarching GCP principles (page 4/14)		In line of listing important points of GCP (ICH on GCP, 1995), it seems very opportune here to demand the implementation of a thorough Informed Consent process – as stated in ICH on GCP, paragraph 4.8 – for all clinical studies, also in post-market studies on and with Advanced therapies.
Section 2.3.3	Delete last sentence on page 7 "It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained." Responsibilities for record retention are provided in section 2.3.2.1 (contracts), section 2.3.3 (archiving) and in section 2.8 (protocol). Including this additional sentence implies additional sponsor obligations for notification of recordkeeping requirements, and these requirements appear unclear and unnecessary.	
Section 2.4.1	Notification of Adverse Events and Reactions The second bullet in the first paragraph (i.e. lack of efficacy reporting) doesn't seem appropriate during the clinical phase of development. In a blinded trial, potential lack of efficacy would identified when the results are reported - not on an individual patient basis. Please clarify and remove to another section if this requirement applies to the long term follow up versus clinical trial phase. In this case, a method for determining individual efficacy response must be specified in the long term follow up plan.	
Sections 2.4.2 (Long Term Follow-Up) and section 2.7 (GCP and Sponsor)	Risk Analysis Both sections mention ongoing risk analysis. During the clinical phase, risk analysis would be communicated via the investigator brochure. What are the expectations for frequency and communication of post approval risk analysis? It should be specified how this guideline relate to EMEA/149995/2008, GUIDELINE ON SAFETY AND EFFICACY FOLLOW-UP – RISK MANAGEMENT OF ADVANCED THERAPY	

Commission européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel - Belgium. Telephone: (32-2) 299 11 11.
Office: BREY 10/152. Telephone: direct line (32-2) 29+ 32 2 265 10 75. Fax: (32-2) 29+ 32 2 296 64 67.

E-mail: Boite Fonctionnelle

	MEDICINAL PRODUCTS	
2.5. GCP and Ethics Committee	mentions the importance of the Informed Patient Consent as a point to consider for the Ethics Committee: The EC should consider the following GCP aspects, which should also be addressed in the information, including written information, provided to the subject: […]" Add to the end of bullet 7 in first paragraph, "including when subjects withdraw from the study".	But the document does not state this process as mandatory for the development and the routine use of Advanced therapies.
Section 2.6 GCP and Investigator/Institution	Because of the long duration of the traceability requirement (30 years), the institution should be responsible for development of a system for long term follow up and retention of records. Bullets 5 and 6 should be revised to reflect this.	
Section 2.7 GCP and Sponsor	Add to the end of Bullet 5 in first paragraph, "including when subjects withdraw from the study".	
Section 2.8 Protocol	The first subbullet under bullet 1 (i.e. "the acceptable range of cell numbers and cell viability") is a CMC (chemistry, manufacturing, and controls) topic as opposed to a protocol topic. It would apply to a cell or tissue therapy that is not a commercial product but for commercial products, CMC information is determined by the manufacturer and is part of the manufacturer's product specification. Also not all gene therapies are cell based. This section should be clarified so information on cell numbers and cell viability isn't expected in all protocols.	
Section 2.8 Protocol At the top of page 12	The bullet on ATIMPs incorporating a medical device states that the protocol should contain detailed information on "evidence of conformity with the essential requirements with the regulations". What does this mean? Detailed evidence of conformity with the essential requirements (essential requirements matrix) is provided in clinical study notifications to competent authorities but this level of detail doesn't seem appropriate for a protocol. This section should be revised to clarify the requirement or removed.	
Section 2.9 Investigator Brochure	Bullet 5, "Information on reporting of lack of efficacy", should be removed (see comment on section 2.4.1) or clarified if related to long term follow up versus clinical trial requirements. In this case, a method for determining individual efficacy response must be specified in the long term follow up plan.	

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E-mail: Boite Fonctionnelle

Section 2.9 Investigator Brochure	Bullet 6: Why is "durability of the associated medical device/biomaterial component" part of the information on (S)AE/SAR reporting?	
2.10. Essential documents (page 13/14):	Timelines for record keeping: clinical trial records – until 5 years after the end of follow-up period, traceability records – at minimum 30 years; Traceability records are generated also during clinical trials and in this respect these time lines seem to stand in discrepancy with each other. Patients involved in clinical trials are exposed to unknown consequences of the particular advanced therapy (e.g. production or use of genetically modified cells/tissue) even after the end of the follow-up period (which is just based on risk estimations)	Thus traceability records without the respective clinical trial protocol and data generated in the trial would give very limited information for further ongoing risk evaluation or mitigation. Therefore, it might be sensitive to keep also the clinical trial records / dossiers as long as the traceability records – 30 years or 1 human generation.

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