European Commission
DG Enterprise & Industry
Unit F2 Pharmaceuticals
45 Avenue d'Auderghem
1049 Brussels

15 October 2008

EBE comments on
Draft Detailed Guideline on Good Clinical Practice specific to Advanced Therapy Medicinal Products

Dear Sir,

I have pleasure in enclosing the comments from the European Biopharmaceutical Enterprises (EBE) on the Draft Detailed Guideline on Good Clinical Practice specific to Advanced Therapy Medicinal Products.

For your information, in preparing these comments we have used the following convention:

normal font:	comment
italic:	original text
bold:	new text
~~strikethrouh:~~	suggested deletions

I would like to thank you for the opportunity to take part in this consultation exercise and hope that you will find our comments helpful and constructive.

If you have any queries or require any further information on these comments, please do not hesitate to contact me.

With kind regards,

Piers Allin
Manager, Regulatory Affairs
European Biopharmaceutical Enterprises

SUBMISSION OF COMMENTS ON:

Draft Detailed Guideline on Good Clinical Practice specific to Advanced Therapy Medicinal Products

COMMENTS FROM: European Biopharmaceutical Enterprises (EBE). Contact person – Piers Allin (piers@ebe-biopharma.org)

GENERAL COMMENTS

1) Overarching Guidance

EBE welcomes the opportunity to provide comments on this draft guidance on the CGP requirements for ATMPs. In general we find it to be well written and appreciate the provision of a set of guiding high level principles to ensure the safety of patients included in clinical trials with ATMPS. These principles address the need for retention of information concerning the traceability and history of batch records (including raw and starting materials) for all ATMPs through to the specific subjects who received the products and who may require long term follow-up. However, the types of ATMP/ATIMPs are quite broad and diverse in terms of level of long term risk to recipients. Specifically, the product type (Cell, Gene or Tissue therapy) and characteristics, will impact on the follow-up required for both recipients and donors. With this in mind, we recommend that this be considered an overarching guideline and that the development of guidance specific to each product type (Cell, Gene or Tissue) be considered. The challenges faced by gene therapy whereby the gene is required to persist in order to deliver benefit are quite different to the transient expression of e.g. some GMO based vaccines. These differences should be reflected in the conduct of follow-up plans. Therefore, it is difficult to apply this guideline without more specific guidance for the different types of ATMPs as Gene Therapy Medicinal Products, Cell Therapy Medicinal Products and Tissue Engineered Medicinal Products.

2) Donor Requirements, Reference to other regulatory documents

The recent Guideline On Follow-Up Of Patients Administered With Gene Therapy Medicinal Products (EMEA/CHMP/GTWP/60436/2007), has a more detailed discussion on the range of GT platforms and their long term risks. This Guideline should be more specifically referenced in Sections 2.3.3 and 2.6 of this current draft. Since this guideline is specific to Good Clinical Practice we strongly suggest that this guideline should include consideration of and reference to existing and planned draft guidance for the Implementation of ATMPs in addition to existing CTMP and GTMP guidance. Provision of information should be avoided that is not discussed and/or differs in focus from those specific guidelines. At the same time, this guideline should address the areas that extend beyond existing CTMP / GTMP guidance and/or donor requirements.

3) Retention Period
The proposed draft requires that the sponsor and investigator should retain records for a 30year period. This retention period does not link to any risk-based analysis of the specific type of ATMP or its intended clinical indication. Also, in an increasingly globalized environment any mandated retention period should align with other Health Authority Requirements (e.g. 25 years in Canada). A clear rationale should be provided for the difference from products derived from animal source material. Furthermore, the proposed retention period presumes that the sponsor/investigator will exist for 30 years. If it is the intent to be able to address health concerns of clinical trial participants in the future we believe that a centralized repository held by a public institution may be more appropriate where the records can be deposited. There are many practical and ethical issues associated with this requirement. As experience with ATIMP is gained and data accumulated, consideration should be given for re-evaluation of the retention period.
4) Tissue Engineered Products
Tissues that undergo only minimal manipulation (like cell selection or separation, grinding or freezing), and are intended for a homologous application to achieve a structural (and not a metabolic) outcome have to comply with regulations on good tissue practice, GCP and donor suitability. For all trials in humans, GCP should apply, but the Clinical Trials Directive (2001/20/EC) may not be directly applicable. A risk-based approach to GMP compliance is indicated. In some circumstances, specific clinical testing procedures for ATIMP will need to be developed for specific ATIMP. Tissue Engineered Medicinal Products often require specific surgery for their application and the surgical technique applied may contribute to safety and efficacy of the product. Therefore, the specific requirements for inclusion of surgery in the development process and eventually the product specifications should also be addressed by this guideline.
5) Terminology
Terminology should be standardised and more clearly defined. e.g. tissue /blood establishment/procurement organisation or animal facility.

COMMENTS ON TEXT

Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
GUIDELINE SECTION TITLE: 2.1 Introduction and scope		
Page 4 Section 2.1 Paragraph 2 Line1	The term “actors” is not sufficiently descriptive.	Delete ~~actors~~ Suggest “**other responsible parties and facilities”**

GUIDELINE SECTION TITLE: 2.2 Overarching GCP principles		
Page 4 Section 2.2 Paragraph 2 Line 1 - 2	It appears unrealistic to assume that responsibility and liability for a long-term safety follow–up can be achieved without the strict rules of a clinical study protocol. A long-term safety follow-up in a clinical protocol must not stand in the way of early efficacy analysis should this be needed. A marketing authorisation can be granted on the basis of efficacy and interim safety analyses while long-term safety follow-up of patients treated in pivotal trials is ongoing.	Replace: ~~*Subjects should be followed-up during the clinical trial both for their own care and to allow data collection as needed.*~~ **Clinical trials should be designed to guarantee appropriate follow-up during and after the collection of efficacy data. The duration of follow-up after the clinical trial should be discussed with the regulatory agency in advance and should be aligned with the specific requirements of the product under development.**
Page 5 Section 2.2 Paragraph 4	It is not agreed that the 'Xenogenic points to consider paper' is fully appropriate for all cells and tissues of animal origin used in the production of all ATIMPs, e.g. cell lines used for production of viral vectors.	Please re-consider this point.
Page 5 Section 2.2 New paragraph	For novel ATIMP, product specific assays are required and these are typically developed during the clinical development program.	Add New point 5: **For novel ATIMP, assay development and validation requirements are expected to occur throughout the clinical development and prior to authorisation**.

GUIDELINE SECTION TITLE: 2.3 Traceability		
Page 5 Section 2.3.1 Line 15	As referenced on the last sentence of this section, a guideline specific to traceability will be generated. Since this guideline focuses on GCP for ATIMPs, this section should be focused on ATIMP accountability, as it relates to traceability.	Rename section 2.3: **ATIMP accountability and traceability**
Page 5 Section 2.3.1	Responsibilities should be defined to ensure traceability from procurement through manufacturing, to release to subject.	Add: **All records are to be maintained to enable traceability from procurement through manufacturing, to subject (not just for those of animal origin)**
Page 5 Section 2.3.1 Paragraph 2	*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 ……..*	Modify as follows: *Where an ATIMP contains human cells or tissues, the sponsor of the trial,* **the tissue establishment, other responsible parties**, *as well as the investigator or institution where the product is used, should ensure that ……..*
Page 5 Section 2.3.2.1 Line2	Guidance text: *"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…"* If the ATIMP is derived from cells/tissues (but does not contain cells/tissues) or uses materials derived from cell lines/tissue cultures (such as vectors), then must raw materials that come into contact with the secondary cultures be traced in the same way as described for the drug product? The sponsor cannot be responsible for the traceability at the subject level due to subject confidentiality. Rather, the sponsor should have responsibility for oversight of all the processes of procurement and manufacturing not just traceability.	Modify: *The system should* ***enable*** *the individual product* ~~*and its starting and raw materials – including all substances coming into contact with the cells or tissues it may contain,*~~ ***to*** *be traced through the sourcing, manufacturing, packaging, storage, transportation and delivery to the investigator/institution where the product is used.* **The system should be able to trace:** - **the product starting and raw materials** - **substances coming into contact with the cells or tissues it may contain** - **substances it may be derived from** - **substances used to manufacture components used in the final form** *Application of the product to the study subject (using a unique*

		subject identifier) or other final reconciliation and disposal or destruction of the products **must be maintained by the investigator site** .
Page 5 Section 2.3.2.1 Paragraph 3	Add post donation requirements	Add reference to existing regulations for donor requirements
Page 6 Section 2.3.2.2	*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*.	Modify paragraph as follows: *The tissue or blood establishment or procurement organisation or animal facility should be responsible for* **determination of donor eligibility screening and** *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*
Page 6 Section 2.3.2.3	The manufacturer should have responsibility to oversee the procurement facility and ensure adequate traceability.	Modify paragraph as follows: *The manufacturer is responsible for ensuring traceability during the manufacturing process* **from the procurement organisation** *up to the release of the finalised ATIMP. 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.*
Page 6 Section 2.3.3 Paragraph 1	*…should keep their parts of the traceability records for a minimum of 30 years…* Defining the time period of 30 years by the expiry date of the products leads to different time points for each patient of an investigational centre when records can be discarded. It would be more pragmatic to define a time point applicable to all patients. See also guideline section 2.6, 2.7. and 2.10	
Page 6 Section	Add statement regarding responsibility in event of discontinuation of product development and/or sponsor ceases	Refer to general comment regarding retention period and need for global alignment. Add:

2.3.3 Paragraph 1	to exist.	"**In the event that product development is discontinued, or the manufacturer/investigator goes out of business or is relocated, arrangements must be made for the transfer of applicable records for the specified retention period, and at least as long as the long-term follow-up of patients. …..**"
Page 6 Section 2.3.3	While the minimum data set to be kept is outlined, it would be helpful to include draft templates which could be added in an Appendix.	Suggest the creation of templates based on the list(s) of minimum data elements for 1) Donor identification, 2) Product identification and 3) Human application identification. Reference these templates in the text of 2.3.2 instead of listing elements.
Page 7 Section 2.3.3	<u>For Donor identification:</u> the Place of procurement is open to ambiguity.	Please define if this includes specific facility/country etc.
Page 7 Section 2.3.3	<u>For Donor identification</u>: Donation records should include a record of donor screening conducted and results. This section should have information regarding donor eligibility requirements, and the maintenance of records of testing conducted together with results.	Suggest to add bullet point: **- Donor Eligibility determination**
Page 7 Section 2.3.3	<u>For Product Identification:</u> Volume or other numerical assessment of amount of product at all levels should be maintained.	Add bullet points: **-Volume/number of tissues/cells.** **-Product identification, sterility testing utilised and results**.
Page 7 Section 2.3.3	<u>For Product Identification:</u> It is possible that more than 1 manufacturer will be involved. e.g. for a cell-delivered gene therapy, the viral vector is made and then the cells are manufactured in a separate process. All establishments need to be identified.	Template/list should allow for/reflect that multiple establishments need to be identified for products involving both cell and gene therapy components.
GUIDELINE SECTION TITLE: 2.4 Safety reporting and long term follow-up		
Page 8 Section 2.4	*See general comments* regarding reference to specific ATMP risk management guidelines.	Focus section on GCP related issues including: 1) Adverse event reporting referencing unique aspects and risk

		management guideline. 2) Highlighting the need for subject consent for long-term follow-up 3) Processes to ensure follow-up of subjects.
Page 8 Section 2.4.1 Line 17 ff	The safety issues of particular concern should be completed with two additional aspects: - mandatory concomitant medication and - medical devices /combined products	Add two additional points: - **Adverse events related to mandatory concomitant medication (e.g. immunosuppression)** - **Adverse events related to medical devices which form part of the product or are used for application of the product** **Differentiated causality assessment concerning the safety issues mentioned above should be implemented in the clinical trial protocol.**
Page 8 Section 2.4.1 Line 17 ff	*Adverse events related to the surgical procedure or other aspects of the product application process* For tissue engineered medicinal products surgery may not only be an application process but very specific surgical techniques often form an integral part of the product.	Modify text: *Adverse events related to surgical procedures* **required by the investigational product** *or ~~other~~ aspects of the product application process*
Page 8 Section 2.4.2	Needs greater clarity. Suggest mention long-term efficacy follow-up as proposed in the RM guideline.	Add 3rd bullet (top of page 9): **- Long term follow-up should be consistent with the Risk Management guideline**
Page 8 Section 2.4.2	Long term follow-up. Will websites/Phone lines be suitable for long term follow up when a sponsor goes out of business or loses funding etc. Websites are notorious for changing or going off line over time.	
Page 8 Section	Subjects must consent to further follow-up in writing and this must be approved by regulatory authorities and IECs	Modify first paragraph as follows: **For each clinical trial,** *the need for and the nature of follow-up and*

2.4.2 Paragraph 1		*if applicable long-term follow-up, after the end of the trial should be determined by the sponsor* **in consultation with the regulatory agency**. The *sponsor should also take into account* **the nature of the ATIMP, the current state of knowledge regarding the ATIMP, the result of a risk analysis, and** any *Community guidance on follow-up of subjects treated with particular types of ATIMPs*. **The sponsor should document the follow-up requirements in the protocol and obtain consent from the subjects and approval from IEC as well as the regulatory authorities.**
Page 9 Section 2.4.2 Line 1	*- follow-up for the purpose of collection of data (which might not be involve all subjects) i.e. safety follow-up and…*	Suggest to modify: *- follow-up for the purpose of collection of* **specific** *data ~~(which might not be involve all subjects)~~ i.e. safety follow-up and…..…*
Page 9 Section 2.4.2 Line 5	The discontinuation of the product development and the possibility that the (former) sponsor ceases to exist as a legal entity should be separately regulated. (see next point)	Suggest to modify: **…..***even in cases where the product development is discontinued ~~and/or the (former) sponsor ceases to exist as a legal entity~~*. **This clinical trial follow-up maybe supported by:** *- websites/phone-lines that….* *- subject alert cards that….* (suggest inclusion of an example of a subject alert card in an Appendix)

Page 9 Section 2.4.2 Line 7ff	The financial protection of the patient follow-up in cases where the (former) sponsor ceases to exist could be achieved by: - all-risk insurance - co-operation with an existing public fund or corporation with foundations like the Michael Fox Foundation, or 'Deutsche Schlaganfall Gesellschaft', who may be willing to take that responsibility - establishment of an industry fund covering this risk.	Add: **In the clinical trial protocol, provisions must also be made to guarantee appropriate patient follow-up for cases where the (former) sponsor ceases to exist as a legal entity.**
Page 9 Section 2.4.2 Paragraph 2	" Subject alert cards that inform treating physicians about product used…..". This section is ambiguous. Is it referring to the process similar to a clinical trial with an IMP where a contact card is provided to subjects so that in an emergency a treating physician would be able to access information about what study drug the subject is taking? If so, the sponsor does not have details of the name of the subject.	**Clarify** the requirement for subject alert cards. If the intention is to provide contact cards similar to cases with IMP, the investigator would provide the subject with a contact card which has been approved by the sponsor and the IEC/IRB. Normally, there would be a 24 hour contact number.
Page 9 line 13	In the former third bullet point information should go to the 'investigational site or the sponsor' rather than the competent authorities.	Modify text: *…, and of the need to inform the ~~competent~~* ~~authority~~ **investigational site or the sponsor** *in the event of certain serious adverse event.*
GUIDELINE SECTION TITLE: *2.5* GCP and Ethics Committee		
Page 9 Section 2.5	Not all items are appropriate for all ATIMP.	**As appropriate for the respective investigational product**, ~~*The*~~ *ethics committee should consider the following GCP aspects, which should also be addressed in the information….*
Page 9 Section 2.5	Doesn't sufficiently cover gene-modification.	Add further bullet points at bottom of page: **- specific safety measures for integrating and/or live viral vectors** **-consultation with Institutional Biosafety Committee"**
Page 9 Section 2.5	The term "traceability" is mentioned twice. It can be found under bullet points # 1 and 5. The context does not sufficiently explain what sort of "traceability" is meant under those specific	Please clarify the term under the respective bullet points ("subject" and "product" traceability).

	points.	
GUIDELINE SECTION TITLE: *2.6* GCP and Investigator/Institution		
Page 10 Section 2.6 Bullet # 4 and Page 11 Section 2.7 Bullet # 4	We agree that the investigator should have knowledge of the risk analysis of the ATIMP and the sponsor is responsible to ensure that its intended use is performed and provided to the investigator. This analysis is prepared as information is gained in ongoing investigations. It should be recognized that risk information is normally communicated to the investigator in the investigators brochure or updates to it and to the patient through the informed consent or updates to it.	Reference the investigator brochure and informed consent as the primary method to ensure communication of risk analysis to the investigator and patient. Add bullet: **- For combined products, the risk analysis and risk management plan of the device part should be shared with the investigators.**
Page 10 Section 2.6 Bullet # 6	It is agreed that there is a need for long-term record retention. However, see general comment and comment on page 6, 2.3.3	Please refer to general comment.
GUIDELINE SECTION TITLE: 2.7 GCP and Sponsor		
Page 10 Section 2.7	There appears to be a lot of overlap with section 2.6 (GCP and Investigator/Institution) and section 2.7 (GCP and Sponsor). Agree that these are required for both but it needs to be very clear who is responsible	Add bullet point: **-(currently) shared responsibility will be documented for each ATIMP.**"
Page 11 Section 2.7 Bullet # 2	Defining the time period of 30 years by the expiry date of the products leads to different time points for each patient of an investigational centre when records can be discarded.	(see comment page 6 Section 2.3.3)
Page 11 Section 2.7 after Bullet 5	Sponsor should confirm the appropriate sterility testing for ATIMPs and that this is maintained through to dispensing to the subject.	Add new bullet: - **The Sponsor should confirm compliance to GMP.**
Page 11 Section 2.7	We agree that training on the use, application, implantation or administration procedures of those ATIMPs that may require	Add: - **Specific application, ~~implantation~~ surgical or administration**

Bullet # 8	specific concomitant therapy and may involve surgical procedures and information on the standardisation and optimisation of these procedures should be provided. Are there specific expectations related to the creation of this training/information? We suggest that this information be provided in an Appendix to the ATIMP protocol.	**procedures should be detailed in an Appendix to the ATIMP protocol.**
GUIDELINE SECTION TITLE: 2.8 Protocol		
Page 11 Section 2.8 Line 1	The document should support unexpected intra-operative decisions.	Add: **-Intra-operative decisions deviating from the protocol, may be made by the surgeon in the best interest of the subject's safety**
Page 12 Section 2.8	Should acknowledge that ATIMP may be released prior to completion of all testing and there must be a mechanism for notification from manufacturer to investigator	Add: **- specific requirements for ATIMP that are released prior to the completion of all testing, in particular relating to adverse event reporting**
Page 12 Section 2.8 Line 10 - 12	More general wording proposed since many more examples for complex blinding procedures are conceivable.	**Detailed instructions to ensure blinding of the trial where needed.**
Page 12 Section 2.8 Line 22	~~Deletion of the two examples (line 23 - 25) is proposed as~~ Suggest different wording as this list may not be complete	Modify text: - Information on any particular requirements for safety reporting **including but not limited to….**
Page 12 Section 2.8 Major bullets # 5,9,11	See general comment on traceability and risk management, this section should avoid repeating specific aspects of long term follow-up, safety reporting and traceability but should include a reference to more specific guidance.	At Bullet 6 (long-term follow-up), **add** reference to risk management guideline. At Bullet 10 (safety reporting), **delete** specific items listed referring instead to Section 2.4.1 and/or the risk management guideline. At Bullet 12 (traceability), **add** reference to specific (pending) guideline.
GUIDELINE SECTION TITLE: 2.9 Investigator Brochure		
Page 12 Section 2.9	The safety issues of particular concern should be completed with three additional aspects:	- *Information obtained from ongoing risk analysis based on existing knowledge of the type of product and its intended use* **including risk**

Line 5	- surgery, mandatory concomitant medication and medical devices	**associated with the application method (e.g. surgery, concomitant medication, devices)**
Page 13 Section 2.9 Bullet # 5 (line 8) # 7 (line 10)	The information on product protection and product disposal should be part of the clinical trial protocol and not of the Investigator Brochure.	~~- information on product protection (storage….~~ - ~~Information on product disposa~~***~~l~~***
Page 13 Section 2.9 Bullet # 6	Avoid multiple and differing references to safety issues.	*Information on ~~the product safety handling, containment~~* **(S)AE/ SAR reporting expected.** (See Section 2.4.1)
Page 13 Section 2.9 Bullet # 10	What is meant by a long-term update?	Please clarify the meaning of "long-term update"
GUIDELINE SECTION TITLE: 2.10 Essential Documents		
Page 13 Section 2.10	Need to better define the relationship between the traceability records and the clinical trial records. Are certain records duplicated to meet these differing requirements?	Please clarify where the original record is to be retained if duplicate records are required. The requirements should be consistent with routine clinical trials standard (2 years after the last marketing application anywhere in the world).
Page 13 Section 2.10.1 Par 2	There is a potential difficulty, to link donor to subject and to ensure compliance with data protection and privacy issues.	Add: **Donor information must be kept confidential with unique identifiers for each donor.**