SUBMISSION OF COMMENTS ON IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION

Regulation (EC) No 1394/2007

Comments on The European Commission Draft detailed Guideline on Good Clinical Practice Specific to Advanced Therapy Medicinal Products
Version 9 October

COMMENTS FROM: EuropaBio
GENERAL COMMENTS
EuropaBio welcomes the opportunity to review this draft guidance on the CGP requirements for ATMPs. In general we find it to be comprehensive, well thought through and written and appreciate the provision of a set of guiding high level principles to ensure the safety of patients treated with ATMPs. The discussion on traceability and long term follow-up was especially useful and the particular issues surrounding the GCP activities specific to ATMPs well delineated. What is missing at this stage, however, is a clearer definition of what constitutes an ATMP and the risk benefit that should be appropriately applied to the different types of ATMP. The types of ATMP/ATIMPs are quite broad and diverse in terms of level of long term risk to recipients - therefore, until further clarification on the definitions and the particular risks associated with each product is provided, it is difficult to see how this guidance should be applied. 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 various GT platforms and their range of long term risks and should be more specifically referenced to in Sections 2.3.3 and 2.6 of this guideline. We would also suggest inserting considerations concerning GCP inspections for ATMPs. Due to the ATMPs specificities as regards GMP, GCP and pharmacovigilance, we would expect that specific groups of Inspectors are appointed for the inspections of activities involving ATMPs. Is this indeed the case?

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Section no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
2.1.	In the definition of “ATIMPs”, a clear differentiation between products legally on the market and ATIMPs is missing. At the moment, sponsors with products legally on the market have to conduct clinical trials to collect data for their centralised MA. It is not defined in which scope these products are ATIMPs. A clear borderline between ATIMPs and products legally on the market is missing. The fact that these products are already administered to patients has to be taken into consideration. Taking this into regard,	

	products legally on the market have to be separated from real “Investigational Medicinal Products” that are used in humans for the first time.	
2.1	"Actors" does not sound appropriate, and it is surprising to see it used in this scientific context.	Replace "actors" by "contributors", "parties" (as used elsewhere in the document) or some other description. Or is it a typo for “factors”?
2.2 point 2	Is this any different from normal CT practice? If not, then should it be mentioned at all? Perhaps it could be, but with explanation that this is normal practice and also applies to ATMPs. If it is not normal practice, then it should be clarified that this is specific practice for ATs	
2.2, 2.3	Traceability of each ATIMP It is not clear how this can be achieved whilst patient and donor data are protected at the same time. Marketing Authorization Holders do not have access to medical records of patients or donors. Patients and donors cannot be obliged to transfer their data to Marketing Authorization Holders or other third parties. In Germany for example this is forbidden by law (Art. 2 Abs. 1 Grundgesetz, German Constitution). But it might be forbidden in other member states, too, du to their national legislation. Apart from that may hospitals/ medical practitioners not transfer any patient data to a third party as this is a criminal offense by national law like e.g. in Germany (§ 203 Strafgesetzbuch, Criminal Act and data protection law etc.). An exchange of patient relevant data would only be possible, if all data were anonymised/pseudonymized. If all data were anonymised/pseudonymized, it is not quite clear, how the system would work efficiently. Pharmacoviligance data might be obtained from different sources: the patient, the hospital, one or more medical practitioners at various times over long periods of time. How should the Marketing Authorization Holder know, that the data are from the same patient, if he received already anonymised/pseudonymized data from patients (e.g. from the patient and later from the medical practitioner of the patient or hospital? How should the Marketing Authorization Holder know that the patient data coming directly from the patient and the data received	Discussions with European data protection specialists and member states’ competent authorities to find a solution: safety concerns versus personal data protection. Change the present guideline in a way to make it compliant with national legislation. It is not acceptable that a guideline contains requirements that are not allowed due to the national legislation of the member states.

	from the medical practitioner are data from the same patient, if these data were anonymised/pseudonymized beforehand?) If the Marketing Authorization Holder receives several sets of data from one patient without having the possibility to find out that these are relating to a common source, these might significantly increase the number of adverse events and might render the medicament unsafe (in the worst case scenario) although this is in fact not the case. E.g. in Germany § 40 Abs. 2a No. 1 AMG (German Drug Act) is saying, that the sponsor and authorities may receive only pseudonymized patient data. The situation in the other member states is expected to be similar.	
2.2.2.	Subject's traceability during and after trial completion by the sponsor could be problematic in randomised/blinded studies. This has also to be considered for information about given treatment.	
2.3	Responsibility of the sponsor The sponsor should only be responsible for the traceability of his own actions (see comments point 2.2 and 2.3). If the sponsor is not the medical institution but the future marketing authorization holder, the sponsor does not have access to patient data, as these are only anonymized or pseudonymized according to current GCP, i.e. the future marketing authorization holder does not receive patient data, so he cannot contact him directly.	The sponsor is only responsible for the traceability of his own actions, e.g. if he processes the cells, then only for cell processing etc.
2.3.1	First line "Imply"	"Implies"
2.3.1	Please provide guidance on the requirement to "continue the maintenance of the traceability system" - how long for, for example? Should this be cross-referred to section 2.3.3?	
2.3.2.1	"Autologous" means that the donor and recipient are the same individual. Is this what is intended here? If not, then should "allogenic" be used?	
2.3.3	It is not realistic to ask the investigator or the institution to keep the traceability records for a minimum of 30 years. Usually records in hospitals are kept about 15 years – thus, to keep records 30 years,	Amend to a maximum of 10 years.

	hospitals have to change their 'in house' rules. For many other reasons it is impossible to ensure that such records are retained 30 years at investigational sites. Could you please clarify the responsibility of the sponsor if this rule is not respected in hospitals or at investigational sites ? A centralized database where the records are deposited may be more appropriate if the intent is to be able to address health concerns of clinical trial participants in the future by having access to records of what they were exposed to.	
2.3.3.	Product identification has to include at least type of tissue and cell/product (basic nomenclature). Is “basic nomenclature” a predetermined set of information that could be used by sponsors? How is it defined? How to determine the impact on quality and/or safety of any products, processing steps etc coming into contact with tissue and cells?	
2.3.3	This type of data collection and exchange is not compliant with European data protection law and standard GCP (See comments concerning point 2.2 and 2.3)	Find a system that is compliant with European data protection law and standard GCP.
2.3.3, last sentence	“It is the responsibility of the sponsor to inform the investigator/ institution as to when these documents do no longer need to be retained” Comment: It should be the responsibility of each party to be compliant with the applicable laws and regulations. There is no reason why the sponsor should inform the investigator/ institution	Delete
2.4.1	“New events related to the conduct….This includes…a significant hazard…such as lack of efficacy…for treatment of a life-threatening disease.” Comment: Efficacy is not intended to be shown in Phase I clinical trial. The first measure should here be the safety/feasibility of the application.	

	There could be cases of trials that will not be able to show efficacy but in maximum a trend. "Adverse events related to the surgical procedure…" Comment: Not every application of an ATIMP needs to be surgical.	Please change "surgical" into "applied"
2.4.2	Long term follow up: If the sponsor is the future marketing authorization holder, he does not have patient data as e g. in the Germany these data have to be transferred in a pseudonymized form (§ 40 Abs. 2a No. 1 AMG (German Drug Act)). The situation in other member states may be similar (see comments concerning point 2.2 and 2.3)	
2.5	"Sibling/parent" pressure – How can that be addressed? "The arrangements for long term clinical, safety and efficacy follow-up;" See comments concerning point 2.4.2 "Risks and precautions related to shedding in the context of …" Shedding is only one feature that could be problematic in gene therapy.	Please change into "The arrangements…safety **and, if applicable,** efficacy follow-up;" Please generalize risk description.
2.6	"The investigator should establish and maintain a system for subject and product traceability" Comment: If the investigator is not the manufacturer for the product, he should only be responsible and maintain the system for his own actions regarding the product. The sponsor should establish and maintain a system for subject and product traceability: there is no reason for having this system twice! There should only be one collection of data. The sponsor should notify serious breaches of GCP to competent authorities.	Amendment: "The investigator should establish and maintain a system for subject ~~and product~~ traceability." Please define "serious breach". Also, this is the responsibility of the competent authority and should not be transferred to the sponsor.
2.8	It is to be noted that for certain trials, the blinding requirement for the person responsible for the administration cannot be met. This	

	will in particular be the case when the two treatments differ in application, e.g. surgical intervention only compared to administration of a cellular product.	
2.10	Record keeping	Amend: maximum 10 years after “last patient out” or final application of ATIMP, whichever is shorter.

Please feel free to add more rows if needed.