SUBMISSION OF COMMENTS ON Draft Detailed Guideline on Good Clinical Practice Specific to Advanced Therapy Medicinal Products

COMMENTS FROM German Pharmaceutical Industry Association (BPI), Matthias Wilken
GENERAL COMMENTS
BPI welcomes the opportunity to review this draft guidance on the GCP requirements for ATMPs. In general we find it to be comprehensive and well written and appreciate the provision of a set of guiding high level principles to ensure the safety of patients treated with ATMPs. Concerning the traceability of products and some other provisions mentioned in the specific comments area there are provisions within the draft guideline that might be of interest regarding patient safety but are not in line with overall legislation concerning personal data protection and requirements in European pharmaceutical law that have to be transposed into the law of the member states. It would be necessary to review the guideline in the light of these differing legal requirements.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Point 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 men for the first time.	
Point 2.2,	Traceability of each ATIMP	Discussions with European data protection specialists and member states' competent authorities to find a solution: safety concerns versus personal

[1] Where available

2.3	It is not clear, how this can be achieved and 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 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	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.

	is expected to be similar. Even Annex I Part I point 5.2 c) of Directive 2001/83/EC states that subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. This means in particular that patient data have to be kept separately as it is not allowed to disclose them to the sponsor. This provision is in contradiction to the requirements that should be laid down in the guideline	
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.
2.3.3.	30 years archiving This is an undue burden to the relevant institutions that are obliged by this regulation, despite that it is unnecessary and not feasible. If e.g. cancer patients were treated, the chance that the data will be needed 30 years after the treatment is highly unlikely. The reason for treating ATIMPs different from other IMPs is not given in the guideline.	Amend to a maximum of 10 years.
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?	

Point 2.3.3, page 7	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.
Point 2.3.3, page 7, 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/feasiblity 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-	Please change into "The arrangements…safety **and, if applicable,** efficacy

	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.	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. Record keeping for 30 years: see comment to point 2.3.3. 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: Definition of "serious breach" is lacking. This is the responsibility of the competent authority and should not be transferred to the sponsor.	Amendment: "The investigator should establish and maintain a system for subject ~~and product~~ traceability." Amendment: record keeping for a maximum of 10 years concerning clinical trials Amendment: There should only be only one collection of data. The system for traceability should be established within the limits of responsibilities of each party. Delete.
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.