Submission of comments on the « Good manufacturing practice for advanced therapy medicinal products »

Company	THERAVECTYS
Type of company	SME (EMA SME status)
Type of activity	R&D and manufacturing of ATMPs

Version number: 1.0

Release date: 12-11-2015

1. General comments

General comment (if any)
THERAVECTYS welcomes the initiative of the European Commission to launch a public consultation before the release of the new document “Good manufacturing practice for advanced therapy medicinal products”. The release of such document clearly reflects the increasing number of Advanced Therapy Medicinal products under development and that more and more will come to the market in the next few years. The fact that there is a distinction in some of the requirements stated in the document between “investigational ATMPs” (intended to be used during clinical trials) and those for marketing authorization (“commercial ATMPs”) is appreciated. To ease referencing to the “Good manufacturing practice”, numbering the sections as they appear in the “Good manufacturing practice” would be appreciated. Missing information - Additional recommendations/requirements might be used or references given to guidelines and binding documents related to the use of ATMPs which are also Genetically Modified Organisms (GMOs); - Labelling requirements and examples of labels could be added or reference to the Good Manufacturing Practice given if no specificity for ATMPs are expected; - The role of the quality assurance in the document management, traceability etc… should be emphasized.

2. Specific comments on text

Line number(s)	Comment and rationale	Proposed changes
94	“Self-inspections” are mentioned as a mean to monitor compliance with GMP. However, no frequency or relevant date are mentioned.	Self-inspections should be performed prior manufacturing of a clinical batch? At regular intervals (at least once per year)?
102	N/A	The reference to the risk-based approach guideline (EMA/CAT/CPWP/686637/2011) would be welcomed here.
104-105	“[…] the risks to the quality of the product are greater when there is a complex manufacturing process”	The risks to the quality of the product increase in parallel to the complexity of the manufacturing process
110-114	It is mentioned that “it is important to recognise some flexibility in the application of the GMP requirements”. However the amplitude and the points concerned remains not clear.	-
121-123	It is mentioned that “While an acceptable level of quality must be ensured for investigational ATMP’s, it is acknowledged that additional flexibility is warranted, in particular for early phases of clinical trials”. However there is no indication on the amplitude and the points concerned by this flexibility.	-
133-137	Training of personnel involved in the manufacturing and testing of the products should be traced as well as training of personnel involved in the cleaning and maintenance.	-
144-146	It is mentioned that “Where necessary, personnel engaged in production, maintenance, testing and internal controls, and animal care should be vaccinated”. What about disease for which no vaccine exists? Is it necessary to screen the personnel? If yes, how the question of confidentiality and ethic can be managed?	-
185-187	It is mentioned that “In particular, to protect the operator	-

Line number(s)	Comment and rationale	Proposed changes
	and the environment, dedicated production areas should always be used for the manufacture of pathogenic organisms (i.e. Biosafety level 3 or 4)". Does this also concerns CQ areas?	
243	"Production areas should be well lit, particularly where visual on-line controls are carried out". Does this means that individual inspection of filled final containers remains mandatory? Final containers for MTI could be one bag per batch. This individual inspection seems still relevant but the conditions and the objectives of this inspection are different from the ones which apply for "classical" glass vials. These conditions and objectives have to be detailed.	-
275	"adequately maintained" is not specific enough	-
317	The instruction relevant to the manufacture of the medicinal product as well as relevant records /reports should be kept and made available upon request of the authorities Can you clarify the life time of those documents?	-
367	It is mentioned that "Release and rejection criteria for raw and starting materials, intermediates, bulk and finished product, including release strategy for characterisation results that are not available prior to product release". Tests for which it is acceptable to obtain the results after release have to be defined.	-
319-419	Adding that the documents quoted below must be written, dated, checked and signed by different persons would be welcomed.	-
335	A written request to start manufacturing a batch must be released but there is no detail on who should write and/or sign this document.	-

Line number(s)	Comment and rationale	Proposed changes
470-473	“In addition to the specifications for the starting materials, the agreement between the ATMP manufacturer and the supplier (including blood and tissue establishments) should contain clear provisions about the transfer of information regarding the starting material, in particular, on tests results performed by the supplier and traceability data.” Does this mean that the manufacturer can rely the acceptance of raw material on tests results obtained by the supplier? If so, does the supplier should be considered as a subcontractor?	-
482	“For cell-based products, where final sterilisation is generally not possible […]”. Other type of ATMPs are also susceptible to final sterilisation (such as viral based vectors).	-
554	The use of cell stocks/banks that were not produced under full GMP compliance is authorised in “exceptional and justified cases”. Does this apply to investigational ATMPs only? Also to commercial ATMPs?	Please add if this exemption applies only to investigational ATMPs.
573	“[…] substantial modifications in the manufacturing process of an investigational ATMP also require approval by the competent authorities”. Examples of the modifications which are considered as “substantial” would be welcomed; or reference to guidelines provided.	Examples of the modifications which are considered as “substantial” would be welcomed; or reference to guidelines provided.
708 – **Q17**	There is indeed an inherent variability in the manufacturing process of ATMPs, whether cell-based or not. For first-in-Human trials or early phases, the manufacturing process might not be validated. However, it is understood that at the commercial level, at least 3 batches of product, at the commercial size, must have been produced. Can the	-

Line number(s)	Comment and rationale	Proposed changes
	European Commission confirmed this fact? In addition, we would recommend that at least the release tests be validated, even though the manufacturing process is not.	
831-835	There is a discordance in the duration of document retention, in particular for cell-based ATMPs for which it is mentioned in §6.5 (line 440) that they must be retained for 30 years.	Homogenise the duration of document retention.
883-885	It is mentioned that "If a significant deviation in the manufacturing process described in the clinical trial dossier 884 has occurred, the event should be notified to the relevant competent authority if the manufacturer wants to release the product." The notion of significant deviation has to be more detailed. It raises also the question of the delays of response from the competent authority.	-
976-978	"Replacement of routine batch testing by process validation. While process validation is usually not required for investigational medicinal products, it may be very important when routine in-process or release testing is limited or not possible". Is the sterility test also concerned?	-
1000-1007	The section on stability applies only to ATMPs which have been authorized. What is the rationale? Stability studies must also be performed on investigational ATMPs.	Add the ICH on stability reference; indicate that investigational ATMPs stability must also be assessed.
Q22	Yes	-
Q23	Yes, otherwise the hospitals pharmacy would not be authorised to thaw, dilute or mix the investigational ATMPs.	-