Comments for Consultation Document:
Good Manufacturing Practice for Advanced Therapy Medicinal Products
Comments from F.Hoffmann-La Roche Ltd

1. General comments

Line number(s) of the relevant text (e.g. Lines 20-23)	General comment (if any)
We appreciate the effort the Commission has undertaken to address GMP aspects, unique to ATMPs and are pleased to be asked to provide input. Our specific comments have been subdivided into general comments and specific comments on text. The following suggestions are for consideration to be included in this GMP document:	
Sections 7, 8, 9, and 10	Nothing said about terminal sterilization and the requirement that it is validated (regardless of stage of development). Suggest adding "Where terminal sterilization is used, it must be validated".
	Currently specifics are distributed throughout the document, but because it is such a different process, there is an opportunity for autologous to have its own section. They represent a unique situation even for ATMPs.
	In some cases pharmacopeia methods may not be suitable due to the type of product, stability issues, or clinical use requirements. It would be important to allow consideration of alternative methods as part of the control strategy.

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Q1	Pointing to a risk-based approach is helpful in enabling product and development phase appropriate flexibility whilst ensuring that specific risks are addressed.
Q2	Risk assessment/management is challenging to do well and more information than is given here will be needed to deliver the required outcome. However, it is suggested that this is not the place to provide this additional information. Instead, provide a cross reference to ICH Q9. Separately, over time, consideration might be given to building a set of ATMP-specific case studies to further support organisations in this area
Q6	Although the 'in general' wording suggests that alternatives are possible, the sentence in Lines 231-233 requiring Grade A with Grade B background is restrictive and does not take account of current accepted practice where isolators are used (Grade C background is commonly used and Grade D background may be acceptable per EudraLex Volume 4, Annex 1, 23), nor does it allow for future technological advances – see comments on Question 8. It should not be assumed that higher standards must apply to commercial products. Particularly for autologous cell/gene therapies where there is no change in the scale of production with phase of development, premises for the manufacture of commercial products may well be the same as those used for investigational products.
Q8	Of fundamental importance is the safeguarding of patients/clinical trial subjects. This applies to all phases of clinical trial and to commercial products. The focus should therefore be on performing a detailed evaluation of risk and mitigation of that risk as appropriate to provide the required sterility assurance, not stipulating specific air classification requirements. It is currently recognised that isolators may operate with background air classification less than Grade B. With adequate controls and risk mitigations (e.g., closed systems), it is feasible that background C or D might be appropriate not only for early phase clinical trials but for pivotal trials and commercial production too. A risk-based approach will also leave open the use of future isolator and closed system technology developments which may allow for further relaxation of background air classification, even to

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	unclassified areas in hospitals, irrespective of phase of clinical trial or commercial production. It is not clear why the question includes "with the exception of gene therapy investigational medicinal products", since we do not see any reason why the above should not apply to ex vivo gene therapy products too.
Q10, Q12 Lines 331-333 addresses change control requirements for IMP Q15, lines 573-574 addresses IMP change control requirements	There are sometimes unanticipated changes needed real-time on the production floor. Change control may be implemented for significant changes and for early stage IMP production, however, there may not be sufficient time to seek Health Authority approval prior to when the patient requires the product. Suggest HA notification may occur as soon as possible after production. (especially needed for atogogous products) We need these waivers. Please advise on where they should be stated; this document or another one.
Q15	In early development less product and process specific knowledge may be known at time of production. New knowledge is gained during early phases and therefore requires some flexibility to make changes/deviations on the floor from what was planned. Acceptable as long as documented and assessed prior to release for use.
Q17	Due to the variability of starting material and its very limited availability (e.g. in case of autologous cells), process validation should be unit operations-based, covering aspects (i.e. equipment, instrumentation, software, operator variability, etc) to minimize variability from the operations point of view. Consider using donors cells for those unit operations that need use of representative material to be validated. In general, validation done using such approach should be valid for a whole class of products (i.e. autologous T-cells based products), as long as process steps are the same.

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Q18	It does not provide information on alternate methods. Lines 417-419 indicate an option for continuously monitored process but the release and QP section does not address this.
Q19	There should be a section around stability and/or setting of expiry/use-by dates for IMPs.
Q23	Yes, we agree that reconstitution is not manufacturing and is therefore outside GMP; this should fall under the remit of general hospital medication preparation by pharmacy, nursing or other appropriate health care professionals. . Suggest changing wording to “development appropriate process for reconstitution….”
Q25	Responsibility for validation of new automated production processes and equipment should belong with the manufacturer holding the CTA or license. Equipment may be "qualified" in early stage development. Processes performed at hospital or pharmacy should be regulated by GCP. Where applicable GMP principles should apply.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 180	Delete "or cytotoxic agents" from line 180. There is no globally consistent definition of cytotoxic agent and is not used in Eudralex Volume 4, Chapter 5. Many oncology products could fall into this category if verbiage left in resulting in facilities that could not be used. This is an unnecessary restriction, would be an undue burden on manufacturers and prevent product from being made in what otherwise would be deemed a suitable facility.
Line 565	In early development less product and process specific knowledge may be known at time of production. New knowledge is gained during early phases and therefore requires some flexibility to make changes/deviations on the floor from what was planned. Acceptable as long as documented and assessed prior to release for use.
Lines 587-588	Verbiage improvement: Propose: The control strategy **should be commensurate with** the risks.
Line 599	Current statement is too proscriptive. Sterilization of articles and materials elsewhere is acceptable provided that there are procedures describing flow of materials into Production areas, such as entry through an airlock or pass-through with the appropriate surface sanitization precautions. Sterilized articles may need to be enclosed in multiple wrappings, as appropriate to the number of stages of entry to the clean area.

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Line 635	Propose to allow for cleaning that is verified for IMP rather than validated (also refer to comment line 648). Once cleaning is verified to be acceptable (line clearance), the risk should be adequately controlled.
Line 648	The current verbiage in the draft refers to "cleaning validation between the manufacture of different batches". Would propose instead to remove validation (cleaning between the batches), and add according to a validated process, or verified according to a risk based approach (which aligns with the proposal below for line 649).
Lines 687-689	As acknowledged in other parts of this document, many cell/tissue based products must be released before final test results are available. Sufficient flexibility should be allowed such that quarantine requirements do not conflict with expedited release strategies. However, that is not clear in the way this document is currently written.
Lines 687-689	Agree with above comment. More flexibility needs to be stated in the document around meaning of "…held in Quarantine…". Currently for IMP we have written procedures that allow for the movement of unreleased IMP material around the Roche controlled network (which may include CMOs) in a controlled manner via the processes of Approval for Further Manufacture (AFM) and Quarantine Shipment. AFM and Quarantine Shipment allows the material to move through the manufacturing process/next manufacturing site in a more efficient and effective manner. It should be noted that material must be fully released prior to shipment to the clinic.
Lines 836-838	Retention requirements should be consistent with Delegated Acts. "Retention for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used, whichever is

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	the longer period."
Lines 1014-1017	In fact the scope of this paragraph would have to be the (primary) contractor, not subcontractor. We should stick with contract acceptor and contract giver terminology only analogous to Eudralex Volume 4 chapter 7. I assume the bold wording below is proposed to be deleted (hard to tell). Subcontractors are addressed in the requirement that contract giver must provide prior approval of any subcontractors.
Line 1020	1. We would prefer to speak to control of the outsourced activities (consistent with Eudralex Vol4 7.4), versus a requirement to review records and analytical results, which could range from a batch to batch basis to a periodic review. 2. This is guideline, so 'must' should be changed to 'should'.

End of comments.