Consultation Document Issued 23 July 2015
Good Manufacturing Practice for Advanced Therapy Medicinal Products pursuant to Article 5 of Regulation 1394/2007

1. General Comments:

As written, the proposed guidance adds very little to what is already provided in the main chapters of the EU GMPs and annex 2. Only section 7 adds any specific definition relevant to ATMPs. Much of this document could be removed with reference to the EU GMPs. Maybe a more logical approach would be to break ATMPs out of annex two and prepare a separate annex that would be much shorter and would deal with specific issues. This would avoid compliance drift in the future as cGMP adapt to best practice across all parts of the health care sector.

2. Specific Comments on Text:

Section	Line number	Comment and rationale; proposed changes (if any)
1	**59-101**	Introduction is confusing and contradictory with regards to requirements/applicability of any ATMP GMP guidance at hospitals. Paragraph one infers that one reason for separate GMPs is because requirements for early phase within a hospital environment are different to those of the pharmaceutical sector but paragraph three would indicate that hospitals are exempt. A common standard, whether within a hospital or pharma for early phase work would be desirable – any variances due to technical challenges are relevant to both environments.
1	**73**	As product/process knowledge increases, some autologous platforms may move from centralized to distributed models to enable point-of-care manufacturing. With that in mind, these guidelines should ideally cover point-of-care/hospital manufacturing as well, including manufacturing in closed automated systems.
Q1	**75**	No comment
Q2	**75**	Some guidance upon the application of a risk based approach would be helpful but reference to existing ICH Q9 guidance would be the preferred option rather than repeating detail here.
Q3	**75**	General comment – where more specific quality systems are in place these should be recognised. Where there are commonalities these should be assessed and a hybrid approach meeting both requirements should be seen as acceptable. Any specifics should be adopted for all quality systems applicable. There would be value in mentioning upfront the special controls needed for ATMP's around donors, cross contamination risk and limits on expansion of donor cells etc. Though this is raised in subsequent sections
2	**81**	Mention differentiation between autologous and allogeneic ATMP treatments?
2.1	**103**	Risks to both quality and safety are greatest when there is a complex manufacturing process coupled with limited product knowledge
2	**122**	Reinforce at this point that safety and product quality are paramount
2	**127**	Mention use of defined SOP's (this is addressed later in the document)
3	**128**	Q4: No Comment
3	**137**	Identify example health risks due to human sourced materials? (Donor, viruses, TSE's etc.).

3	**147**	Address the cross contamination aspect that relates to human-sourced materials
4	**157**	Q5 : No comment
4	**157**	Q6 & 7: Any additional flexibility should be justified using a risk based approach. This should be equally applicable to early as well as late phase/commercial. The degree of risk/ mitigation at early phase should support a different approach.
4.2.1	**184**	Show examples of dedicated productions areas? In the context of autologous therapy this could be a more hospital environment than GMP manufacturing facility?
4.2.1	**188**	In addressing cross-contamination, autologous manufacturing could inherently be considered multi-product.
4.2.2	**208**	Is the aseptic environment meant to foresee manufacture in a hospital environment in the (distant) future? For example a fully contained automated sterile device or container used for processing autologous products at the patient bedside?
4.2.2	**233**	Q8: Use of a Grade A operating area in a Grade C/D background should be possible where supported by a justification that considers all potential risks, mitigations and data that demonstrates that the product is adequately protected. This justification should be applicable across all phases and not just early development where appropriate. Within the R&D sector there is significant evidence that aseptic technique is maintained under such conditions with appropriate training, qualification and defined processes.
4.3	**261**	This section should include some guidance on storage of process intermediates e.g. human cells and special precautions needed.
5	**273**	Q9: Lines 285-287 discuss various types of water that can be used. This, as is, is confusing. What types of water are allowed within the process at which points? Why is Water For Injection not included in the discussion here?
5	**281**	The guidance on use of disposable equipment could be stronger than 'where possible' due to the particular risk from human products for this type of manufacturing process.
6	**299**	Q10: With regards to specifications for raw materials of biological origin (lines 342-344). No mention of TSE/viral status is made. This should be included as part of the assessment for these materials.
6	**299**	Q11/12 no comment.
7	**442**	Q13 no comment
8	**515**	Q14 No comment
9	**559**	Q15: Production. Some of the specific information is outdated and a more general reference to risk based approach would be more appropriate. For example lines 652-653 indicate that containment of centrifugation steps is necessary. This should be changed to recommend that such process steps are contained unless a risk based assessment of the equipment used indicates that the risk of aerosols are controlled
9.3	**618**	More detail is needed around preventing "mix-ups of dedicated (autologous) materials", as many of the examples highlighted further down are most applicable to allogeneic therapies
10	**708**	Q16/17: No comment
11	**728**	Q18: Certification by the QP does not mention the need to certify investigational IMPS against the Product Specification File are required for IMPS. Is this a deliberate omission or an error?
12	**886**	Q19: Section 12 Quality Control It should be noted that in some smaller units, and considering the

		technical nature of the work, individual management may not be specifically dedicated to a QC role. In such cases a member of management who is independent of production operations for a specific project can provide suitable independent objective appraisal. With regards to records to be kept, the detail should acknowledge that alternative methods are available for recording requirements. For example LIMS may be used where personnel identification is by user number, not initials.
13	**1008**	Q20: (Section 13, Outsourcing) The section is a good example where cross-reference to the main EU GMPs would be a good example rather than trying to repeat the requirements of cGMP in a separate document.