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Comments on European Commission consultation document on GMP for ATMPs

Section	Question	Line	Comment
-	-	-	General comment: The consultation document covers the GMP requirements for both commercial ATMPs and investigational ATMPs. Whilst the document does detail differences in the proposed GMP requirements for commercial verses investigational ATMPs in some sections it is felt that the manufacture of commercial ATMPs should be considered distinct from that of investigational ATMPs. Therefore, it is felt that whilst unlicensed ATMPs (investigational) may be given some latitude in terms of compliance with the strict conditions of GMP, the licenced ATMPs (commercial) should be required to adhere very strictly to the requirements of GMP. To the extent that as ATMPs are more complex and have less clearly understood biological modes of action, they require more, not less, rigorous adherence to GMP standards.
1	-	63-64	Change to "…early phases of research may take place in a hospital or academic setting…"
2.1	-	126-127	Delete this sentence. It is superfluous. Under what conditions would a manufacturer *not* consider all the potential risks?
4.2.2	-	212-214	Should this be: "If terminal sterilisation of the finished product is not possible…"?
4.2.2	-	214-215	"For commercial production of ATMPs, the premises should be fully validated". This implies that, for IMPs, the premises need not be fully validated. Guidance should be provided on the lesser extent of validation required for IMPs.
4.2.2	Q8	-	We strongly agree that a background of C should be allowed for early phases of clinical trials. This would bring the EU into line with the USA, where manufacture of cell and gene therapies for early-phase studies typically takes place in Biological Safety Cabinets (not isolators) in the equivalent of a Grade C background. The higher requirement currently specified in EudraLex Volume 4, Annex 1, puts the EU at a comparative disadvantage in relation to clinical research using ATMPs. If, as we feel should happen, Grade C background is allowed for early phase clinical trials, then gene therapy IMPs should be treated in exactly the same way as other ATMPs. There would be no logic to requiring a higher standard for gene therapy IMPs. Environmental grades described in GMP have no relationship to the extent of containment required.
6.5	-	438	Change to "For human cell-based products…"
9.3	-	640-645	For the manufacture of viral vectors and gene therapies, manufacturing should be separated from other areas. "The arrangements for separation should be demonstrated to be effective". For viral vectors and gene therapies, separation is only necessary for certain steps, namely when vectors are being handled and when post-transfected cells are being handled.
9.3	-	648-649	Change the last sentence so that cleaning validation is only required for commercial production. Cleaning verification is required for IMPs.

12.3	-	957	Further explanation should be given on the level of validation of QC assays expected at the early stages of development e.g. first-in-man clinical trials compared to that required for pivotal clinical trials or commercial ATMPs
15	-	1058-1060	Emergency plan for dealing with accidental release of viable organisms. We agree that it is advisable to have such a plan in place.
16	Q22	-	We agree that, where reconstitution of the finished ATMP is required, the manufacturer's responsibility is limited to the validation of the process of reconstitution and the transmission of detailed information about the process of reconstitution to the users. By the time the ATMP is reconstituted, either at a pharmacy or at the patient's bedside, it is under the control of pharmacy or clinical staff, it is not under the control of the manufacturer.
16	Q23	-	We agree with the principle that reconstitution is not manufacturing and therefore is outside GMP.
16	Q24	-	For ATMPs, the definition of reconstitution provided in EudraLex Volume 4, Annex 13, should be widened to include mixing with an adjuvant, immediately prior to administration.