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EUCOPE comments on the Consultation Document on Good Manufacturing Practice for Advanced Therapy Medicinal Products

No	Lines	General Comments
		EUCOPE welcomes the European Commission's intention to develop Guidelines on Good Manufacturing Practices for Advanced Therapy Medicinal Products (ATMP).
No	**Lines**	**Comments**
1	63-65	EUCOPE acknowledges that early phases of research may take place in a hospital setting operating under a quality system different from the quality system typical of the pharmaceutical sector. However, in order to avoid any misunderstanding in relation to different requirements for clinical trials EUCOPE suggests to include an explicit reference to Recital 81 of Regulation (EU) 536/2014 which states the following: "In order to maximise the valuable contribution of such non-commercial sponsors and to further stimulate their research but without compromising the quality of clinical trials, measures should be taken by Member States to encourage clinical trials conducted by those sponsors."
2	69-72	EUCOPE proposes to replace the term "commercial ATMP" by the term "authorised ATMP" since the term "commercial" is not a regulatory term. Thus, a respective use could lead to misunderstandings, e.g. that those requirements are not valid for products that are not commercialised - e.g. in a non-industrial setting - although they need to be centrally authorised.
3	75	Q1: Yes. Q2: No, since a specific Guidance on this topic is available. Q3: The JACIE accreditation system provides a very detailed set of standards. It can be considered as a suitable standard to help assessing safety and reproducibly processing and testing cellular products if applicable.
4	128	Q4: Yes.
5	157	Q5: In general, yes. However, EUCOPE recommends a reference to Annex 1 EU GMP for microbiological limits and definition of grades. Apart from that, the information in line 232 is vague as it implies early stage trials can be performed in a different environment. It is not always known upfront if a trial will be a pivotal study or not. In general, there should be some reference to the potential use of isolator technology as this is an area of interest for the manufacture of ATMP's from both an aseptic and

		containment perspective. Furthermore, EUCOPE suggests a clarification on the term “large scale production”. Q6: EUCOPE suggests a definition of “closed system” to have a clear demarcation to open systems. Q7: No.
6	231-233	Q8: The use of automated functionally closed systems, sterile tube-tubes welding, spiking with sterile filters etc. should reduce the clean room area to grade C or D.
7	246	The air quality of the clean area has to be defined. Moreover, usual GMP-handling of this issue shall be followed (e.g. drains in non-production areas class D are common), as there is no reason for ATMPs-specific addressing.
8	273	Q9: Yes.
9	299	Q10: In general, yes. Nevertheless, the term “Product Information” could be misleading as it is widely used for the documents accompanying the product upon shipment. The statement in lines 337 to 339 is welcomed. In lines 417-419, the note is unclear. In addition, EUCOPE seeks clarification on the 30-year traceability requirement for cell-based products (line 438). Q11: No. Q12: The requirement for a contract and quality agreement for each biological raw material should be risk based.
10	345+351	For some types of materials (especially fresh cells suspension, thawed products) the requirements stated in the lines 345-351 are not appropriate: Firstly, the storage period of starting materials is not known, especially in the early part of the development. Secondly, in some cases the uniqueness of the starting material (e.g. autologous starting material) requires the manufacturer to use it. Consequently, it is suggested that line 345 is amended in the following way: “Specifications for starting materials **(where applicable)**, including: (…)”
11	426-441	The compliance with other document sources (GMP, GCP, national and EU) needs to be ensured as there are many documents stipulating timelines for archiving of the documents.
12	442	Q13: In general, yes. However, line 452 should read “5.2.12. RAW MATERIALS FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS” (currently in draft). The acceptance of licensed establishments without an audit requirement is fully endorsed (lines 466 subseq.).
13	448-449	The definition of the “release” should be clarified (whether it is applicable for the release for manufacturing or for the release of the product itself). Often, starting material for ATMPs are biologics like blood stem cell products, which have been already tested and released as a drug. Please also note that, the necessity of quality control of the release of the starting material can be logistically challenging. Some of the biological starting material can be very time sensitive and any additional release step might jeopardize quality of the starting material. We understand that there is a need for sufficient control measures. However, we believe the control can be performed by the manufacturing technician prior the start of manufacturing.
14	466-469	The applicability of the audit of blood and tissue establishments remains

		unclear: (i) does the ATMPs manufacturers not need to perform any audit in such an establishments or (ii) is an audit necessary (e.g. Quality System) and lines 466-469 mean that “donation, procurement and testing” should not be a part of this audit.
15	515	Q14: Yes.
16	559	Q15: In general, yes. However, in line 611 “preferably in a standard format throughout the facility” should be removed. There is evidence to show that changing the style and appearance of different labels can reduce errors. EUCOPE seeks evidence for the statement in lines 652-653.
17	644-645	EUCOPE suggests using the different vectors for different CAR-Ts (functionally separated from each other by closed procedures) in the same area (same area is defined “within same walls”).
18	648-649	Line-clearance as usual GMP-behaviour should be sufficient if there is no carryover risk.
19	708	Q16: Yes. Q17: Yes. EUCOPE appreciates this pragmatic approach. For early stage development prospective validation may only be possible using simulated starting material or that from healthy donors and this may be different from starting material used to manufacture product for clinical use. A concurrent validation approach may be more applicable with regular reviews of data from the manufacture of clinical lots.
20	728	Q18: Yes.
21	886	Q19: No. There needs to be more flexibility with respect to the independency of QC from production, specifically in relation to very small-scale manufacturing of investigational ATMP's. EUCOPE suggests that QC activities must be performed by a trained individual independent of that specific production activity. Furthermore, flexibility is needed for samples regarding the manufacturing of individualised patient product where a single or very few units are produced. The retention and reference samples cannot always be fully representative since an individual patient product only one unit may be manufactured. In line 928 the retention of primary packaging and some expensive (non-biological) reagents ordered and made on demand is a huge burden and of very limited value and due to sampling constraints (one item only) rarely helpful in quality defect investigations. Regarding lines 938-943, EUCOPE submits that (usually) starting materials for ATMPs are biologics and mostly limited in size and availability (e.g. biopsies). EUCOPE suggests that samples of starting materials shall be retained (or not retained) according to (i) the individual process and (ii) the risk management of the manufacturer.
22	1008	Q20: Yes.
23	1035	Q21: Yes.
24	1061	Q22: Yes. Q23: Yes. Q24: The thawing, warming, cooling, diluting, stirring, transfer to infusion bag, syringe shall be considered as reconstitution but not buffer exchange.
25	1062	Q25: The automated production raises many questions. It would therefore be useful to have a separate scientific discussion on this topic. The development of automated single-use technologies does not only effect ATMP-development and – manufacturing, it affects the premises.

		Together with the automated closed-systems “ballroom” facilities are evolving as an alternative concept to classical plants. Since automated single-use closed systems protect the product and the process from the environment, ballroom plants need less segregation and less classified containment to manufacture different products simultaneously – the final products are mostly patient-specific without need for upstream and downstream processing. High control of contamination/cross-contamination through the closed system is the main driver of this concept. Together with these novel multipurpose ballrooms and automation as quality improver per se, manufacturers have greater flexibilities in responding to frequent product changes, which are not unusual for complex esp. investigational ATMPs, so premises and manufacturing could “follow the biology” faster and more easily. Innovative therapies need these favorable smart environments and automated systems to contribute to smaller footprints, reduced costs and faster start-ups, thus ultimately enabling promising therapies for patients more quickly than conventional concepts. In general, there should be no objections against a closed-system manufacturing in Class C or D with remaining open steps handled A in C or D, as long as the process has been validated, risk-assessed and media-fill-tested. Even point-of-care models in less classified but controlled environments should be regarded as valid future concepts for ATMPs. Such devices should be installed by qualified personnel from the supplier incl. IQ/OQ documentation where possible. An annual service and/or calibration should be performed which, alongside in process controls and strict quality specifications, should ensure correct performance of the device. However, the process must be thoroughly assessed for risks especially remaining open procedures that could affect the closed system status - the linchpin of the whole concept - must be addressed carefully (eg. due to IPC/QC sampling, preparation of buffer/media, buffer/media exchange during processing, final formulation etc.). A sophisticated barcode-label-documentation system or equivalent to prevent mix up of materials (starting and raw materials, excipients, final product) including IPC-, QC- and backup-sample handling is also required. National blood banks could be a reference for this.

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