EuropaBio comments on European Commission Consultation Document ‘Good Manufacturing Practice for Advanced Therapy Medicinal Products’ Issued 28-Jun-2016

Ref. http://ec.europa.eu/health/files/advtherapies/2016_06_pc/2016_06_draft_guideline.pdf

EuropaBio, the European Association for Bioindustries, promotes an innovative and dynamic European biotechnology industry. EuropaBio and its members are committed to the socially responsible use of biotechnology to improve quality of life, to prevent, diagnose, treat and cure diseases, to improve the quality and quantity of food and feedstuffs and to move towards a biobased and zero-waste economy. EuropaBio represents 77 corporate and associate members and bio regions, and 16 national biotechnology associations in turn representing over 1800 biotech SMEs. EuropaBio’s Healthcare Council represents both large biopharmaceutical companies and biotech SMEs developing medicines, vaccines and diagnostic tools using biotechnology in their development or manufacturing processes.

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General comment(s) if any :
- In general the specifics around GMP requirements that are not changing when applied to ATMPs (like training requirements, Production area design, documentation, etc.) should not be repeated. Instead the reference to existing regulations should be made and only points where either a different application is contemplated, or a relaxing of the requirement should be mentioned in this document. This will avoid redundancy and contradiction to existing requirements. In addition, for companies in the Pharmaceutical Industry who already produce products according to cGMP, the existence of different standards would create confusion and un-necessary complexity. - To address the above mentioned challenges, EuropaBio would welcome a multi-stakeholder meeting. Advantages and disadvantages of a stand-alone document versus an Annex to EudraLex Volume 4 could also be discussed during such a meeting.
- Traceability, while the document addresses this topic in section 6.6 with respect to traceability of cell/seed stock, there is very little mention concerning the need to maintain a chain of identity of donor starting material of cell & gene therapy products through their manufacturing process to their distribution.

Specific text comments

# section	Line no.	Comment / Rationale	Proposed change / suggested text	Classification **L**= low **M**= medium **H**= high
2.1	151-154	Challenges are not limited to auto/matched allo products but apply to some allo as well	Remove reference to auto/matched allo: "In addition, the manufacture and testing of ~~autologous~~ ATMPs ~~(and allogenic products in a donor-matched scenario)~~ poses specific challenges and the strategies implemented to ensure a high level of quality must be tailored to the constraints of the manufacturing process, limited batch sizes and the inherent variability of the starting material."	L
2.1	164-170	Does this mean that hospitals and academic institutions need to have a robust risk management system to complement their quality systems, to an extent similar to that of industry? Additional clarifying language is needed here.		
	167	Typo (word choice) "The risk-based approach is applicable in fashion to all type of operators"	Suggest: " … is applicable to all types of *operations* or *settings*"	L
2.3.2	263-264	It is unclear if the use of alternative methods (i.e. rapid methods) are allowed to generate final results	Please clarify	M
2.3.2	268-269	How does one determine whether a visible particle is foreign in a sample of cells in suspension?	Suggestion – include the following text Characterisation data and understanding of the ATMP's particulate properties needs be accounted for when defining the appropriate tests for visible foreign particulates in the product. Alternative approaches may be required to validate a process with additional controls performed at precursor steps to the final product.	
2.3.3	293-302	There appear to be contradictory statements. The section states that a risk-analysis study should be conducted when manufacturing operations take place in	The classification of manufacturing areas should be based on risk. All manipulations of open product should be performed in a Grade A environment. The	H

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		an open environment in premises other than a critical room of grade A in a background clean area of grade B but also states that under no circumstances it is acceptable to conduct manufacturing operations in premises with air quality classification lower than a critical clean room of grade A in a background clear areas of grade D.	background environment should be Grade B unless the Grade A environment is itself a closed system (eg. Isolator). Then a Grade C background is acceptable.	
2.3.3	300-302	Is this applicable only to products with no substantial manipulation? (A with D background). This appears to conflict with lines 2174-2176 regarding automated equipment.	Please clarify requirements, particularly with respect to expectations of operations performed in an isolator or with automated equipment.	M
2.3.4	322-327	Please see comments above directed towards lines 293-302		H
3.2	398	A “working session” is not clearly defined	Please clarify if this implies a work shift change or everytime one goes into the BSC.	M
3.4	430-432	Text here is confusing. Consider suggested text.	In small organisations, where teams are multi-skilled and trained in both QC and production activities, it is acceptable that a person is responsible for one of these roles (production and quality control) for a given batch, and may fulfill the other role for a subsequent batch. At no time will it be acceptable for a person to perform both of these roles for a single batch.	
4.1.f	454	Specifies only pesticides and herbicides	Should this also include allergens as well, e.g., Penicillin?	M
4.2	468	Materials from infected donors should be segregated	Please clarify if this requirement implies for the need for infectious agent testing of all starting cell material (autologous and allogeneic)	H
4.2	472-474	Where no separate production suites exist, they can be performed with thorough cleaning and decontamination	Please clarify how separation to be handled in cases of no separate suite	M

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4.2.2	516-519	There appears a contradiction, this sections states class A in B background required but earlier in document A in C is stated as acceptable	Please clarify.	H
4.2.2	533-535	Where disinfectants are used, the cleaning regimen should also ensure that residual cleaning agents/disinfectant are sufficiently removed to minimize product contamination	Suggest to include in this section. Alternatively, may be included in cleaning validation (Sec. 10.2)	M
4.2.3	542	It is not clear what is meant by “airflow direction” for the Environmental Monitoring program	Please clarify, does this mean unidirectional flow is a requirement for Grade A and B áreas? In other classifications it is not required.	M
5.2	684	Production should not be restarted until it has been verified that the area has been adequately cleaned and environment is in control	Suggest to add that "environment is in control and should be verified (EM status)"	M
6.3	840	Address Change Controls	Please clarify or confirm whether changes affecting batches are formally approved prior to release of the batch.	H
7.2	931-933	It is not clear if this mean all tissue culture media used in ATMP production requires a functionality (growth performance) test prior to release? At what stage of product development will this apply?. This would be problematic for short shelf-life supplemented media.	Please clarify	H
7.2	952-959	This section is not consistent with basic GMPs which require confirmation of supplier’s test results on some routine basis and require identity testing of minimally critical raw materials.	Plese ensure consistency with GMP requirements	H
7.2	957-959	“For authorised medicinal products…the certificate of analysis is not required Based on the earlier version of this document, we believe the intent here is to state “confirmation of the accuracy of the supplier’s Cof A is not required.	Suggested change: “”For raw materials that are authroised as medicinal products (eg. Cytokines, human serum albumin, recombinant proteins) verification of the accuracy of the supplier’s CofA through periodic independent testing is not required	M

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			and the supervision of the supplier may also be adjusted to a lesser level proportionate to the risk.	
7.2	974	It should be stated that raw materials which have an effect on the product but not intended to be in the final product should be verified as removed	Please include as an expectation for materials that are not intended to be in the final product , e.g., benzonase, beads, etc.	H
7.3	997-999	Audits of blood centers not required per this section, but what about requirement of quality agreements?	Add clarification on quality oversight expectations for blood and tissue establishments (Annex 2 Line 36 of EU GMP)	H
8	1075-1076	It is not clear what is an "appropriately controlled environment" for manufacture of seed lots/cell banks?	Recommend to refer to existing cell bank regulations for environmental requirements. ATMP/viral banks/seed lots should not have different requirements.	M
8	1122-1133	For some AAV manufacturing systems, original cell stocks used to generate cell banks for helper virus production may not have been established under GMP (although their cell banks will have). Such materials are far upstream from the final product, since the helper virus is subsequently used in another cell culture step. The acceptability of cell stocks (not banks) generated without full GMP compliance should certainly be a risk-based determination, but it should not be characterized as 'exceptional.' This scenario may be more common than the guideline's language suggests.	The establishment of new cell stocks/banks and viral banks seed stocks should be done in accordance with GMP. ~~In exceptional and justified cases,~~ However, it might be possible to accept the use of cell stocks/cell banks and viral seed stocks that were generated in the past without full GMP compliance. In these cases, a risk analysis should be conducted to identify the testing requirements necessary to ensure the quality of the starting material.	
8	1129	Should include the expectation that history and traceability of cell stocks/banks as far back as possible should be performed whether GMP or non-GMP.	Please include	H
9.1	1162	Impact of the deviation on the lot should be assessed	Please include	M
9.2	1172	Identity testing of minimally critical RMs is a basic GMP requirement. This concept should also be applied to ATMPs	Ensure consistency with basic GMP requirements	M

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9.4	1211	Consideration should be made to highlight that risk of personnel flow for multi-product facilities. It should be considered that operators could be required to enter a number of production areas during a shift which contain different products. The risk of cross-contamination should be considered and "dirty workers" should not be allowed to enter areas with other products during the same shift.		
9.5.1	1271-1274	Typo – word replacement: …"a manufacturing activity in a clean room which houses an *incubator*…." Section is discussing isolators.	Revise incubator to isolator	L
9.5.2	1328	Allow for risk assessment or justification if filter integrity is not performed before use	Impact of filter integrity testing on a sterile filter before use should be considered. Recommend flexibility to permit Risk-Based Assessment approach.	M
9.5.3	1346	Incubation times for aseptic simulations are defined in the aseptic processing regs, validation protocols should follow the requirements in the regs and not be specific to a fill or protocol.	Please ensure consistency with existing aseptic regs	M
9.5.3	1331-1367	Entire section: The aseptic process verification should take into consideration all of the factors that influence the study, from design to risk mitigation for the product. It is important that all steps and manipulations be simulated, and that all operators be qualified through media simulations. However, applying the standard frequency for process simulations as one does for parenteral products is not sound reasoning. The risk of filling thousands of doses and sampling a small portion of the filled vials for sterility is a very different risk profile than filling individual patient batches and sampling each filled unit for sterility. The sponsor should take into consideration the use of process		H

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		simulations to ensure the environment, people and process continue to work together to keep sterility assurance high, and set the frequency appropriate to the risk. Of course if product is released prior to a sterility result the risk profile is the same as for parenteral products and should mimic that frequency.		
10.1.1	1459	ISO 14644-2 does not cover equipment requalification, covers cleanroom.	Please clarify that equipment should also be re-evaluated because not all equipment is done according to ISO 14644-2.	M
10.1.2 (b)(i)	1476	It should be included that instruments are appropriately calibrated and proper alarms, if any, are in place	Does not mention any alarms checks	M
10.1.2	1493	A mechanism to address equipment of like design and purpose are matrixed for Performance Qualifiation should also be considered.	Suggestion. "Where functionality of the equipment is not affected…without the need to repeat the relevant elements of the IQ/OQ at the manufactureer's site. *In a similar way, if equipment is of like design and purpose (eg the same make and model of an incubator) the equipment can be considered as a group and the performance qualification is performed on a representative item of the group.*	M
10.2	1502	This section does not address decontamination validation. For example, contact time with disinfectants, etc should be addressed as well	Propose to include	M
10.2	1548	The text does not specify batch number rate (three batches per year?)	Please clarify	M
10.3	All (1551-1631)	Clarify timing for PV – when during development must this be completed.	Please include.	M
10.3	1615	It is not clear whether qualification of individual steps is a requirement in addition to using quality markers in place of PV.	Clarify whether individual steps must be qualified, or only steps where no quality markers are available.	M

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11.2	1674-1683	Import testing for batch release of ATMPs should be the exception. The limited volume of the product, the individualize nature, and the uniquness of the testing makes it difficult to perform "full qualitative and quantitative analysis of the active substances" and a benefits from a mechanism to accept the testing in the third country. More emphasis on this scenario is needed in these GMPs	Please expand on the checks and controls expected to be in place to ensure satisfactory quality without reliance on "the re-testing strategy".	H
11.2	1687	QP must not only check conditions of storage and transport but also chain of identity of the product prior to release.	Propose to include	H
11.3.1	1766-1767	The guideline mentions that the step iii "assigning the release status" can be done by the QP or afterwards by another person. In case of investigational ATMPs, it could be a sponsor representative (or legal sponsor representative) as indicated in line 1773 but could "another person" have another role? If yes, should it not be clarified / specified?	N.A.	L
11.3.1	1775	Typographical error, "one trial side" to "one trial site"	Correct spelling	L
11.3.2	1798	There is no mention of any requirement for "look-back" procedure for batch release which occurs prior to results of quality control tests.	Propose to include as a requirement	M
11.5	All (1808-1817)	We presume that this Administration of Out-of-specification products is specifically for investigational ATMP. Please clarify	Clarify the scope of administration of OOS batches.	M
12.1	1836-1838	This sentence seems to require an identity test for each batch to match product to patient (starting material to recipient). Is this an analytical assay or is something like a label check acceptable?	Clarify expectations based on documentation or testing,	H
12.2.2	1864-1865	(retention samples of a fully packaged unit from a batch of finished product). It is unclear what is	Consider clarifying the expectations for retention samples in the context of ATMPs.	H

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		considered primary packaged vs. finished packaged product for ATMPs. And in general the distinction is likely not so important as it is for traditional pharmaceuticals. In the case of ATMPs the retention sample should be available incase of suspected mix-up or break in chain of identity, so the retention sample should be a sample from the final product, labelled as the final product and stored under appropriate storage conditions. The amount should be sufficient to be able to confirm identity (at the batch level, not only at the product level).		
12.3	1937	Typo –critically should be *criticality*	Please revise	L
12.3	1958	What are the validation requirements at the receiving lab?	Include validation requirements in assay transfer.	M
12.3	1958-1970	Method transfer is described only.	Propose to include additional parapgraph for addition / substitution of manufacturing site.	M
12.4	1971-1989	This section does not address in-use stability once frozen product is thawed	Propose to include as a requirement	M
12.4	1984-1989	For ATMPs, the on-going stability program has unique challenges. Given the autologous setting where one patient is one batch and where the product is "sold" for treatment, manufacturing a batch , or putting a portion of a batch on stability annually may not be feasible. Consideration should be given to the storage condition. For example if the ATMP is "fresh", a program of continued process verification and an assessment of storage and/or transport temperature excursions on the quality of the final product could be considered in leiu of on-going stability. Alternatively, if the product is cryo-preserved and has months-to-years of data supporting the acceptability of the storage condition,	Consider situation where on-going stability assessment could be replaces with other types of studies.	H

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		consideration could be given to waiving the requirement for on-going stability and rely on the continued process verification to ensure the production process remains capable of producing product of acceptable quality.		
15	2054-2073	This topic is covered by existing EU GMO guidelines	Suggest to cross-reference appropriate guideline (EC2001/18 Directive, CHMP /GTWP/125491/06 and EMEA/CHMP/473191/06)	M
17	2116-2129	It is unclear whether this applies only to a fully automated process, or to automated steps in a manufacturing process that is not fully automated.	Please clarify	L
17.5	2186-2192	This section does not apply to automated steps in a mfg process not fully automated	Please clarify	L
		Please add rows as necessary (with "copy and paste" empty rows)		