Assobiotec contribution to the European Commission Consultation Document 'Good Manufacturing Practice for Advanced Therapy Medicinal Products' Issued 28-Jun-2016

Assobiotec is the Italian Association for the Development of Biotechnology. It was founded in October 1986 within the Italian Federation of the Chemical Industry (Federchimica) to foster, support and defend the development of biotechnology in all its application fields, such as: human and animal healthcare ("red biotech"), agriculture and nutrition ("green biotech"), environment, processing industry, biomaterials, bioenergy, construction industry, restoration ("white biotech"). The Association currently represents more than 130 companies and science & technology parks operating in Italy. Assobiotec publishes every year the Bio in Italy Report.

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General comments
The current text may conflict with other existing frameworks (e.g.: the general GMP, the mutual recognition and the GMO frameworks). In order to avoid uncertainties and confusions and in line with the principles laid down in the Better Regulation Agenda, Assobiotec believes that more attention should be paid to the existing overlaps. Burdensome duplications must be absolutely avoided, in order to enact an effective and fit-for-purpose framework.

Section	Line(s)	Comment/Rationale	Proposed change/Suggested text	Priority H=high M=Medium L=Low
2.1	167	Typo	**In the text:** "The risk-based approach is applicable in an equal fashion to all type of *operators.*" **Correction:** "The risk-based approach is applicable in an equal fashion to all type of *operations.*"	L
2.2	172-175	Risk-based approach is necessary and not optional.	**In the text:** "The risk-based approach ("RBA") *permits the manufacturer* to design the organisational, technical and structural measures that are put in place to comply with GMP -and thus to ensure quality- according to the specific risks of the product and the manufacturing process." **Proposed change:** "The risk-based approach ("RBA") *is necessary for the manufacturer* to design the organisational, technical and structural measures that are put in place to comply with GMP -and thus to ensure quality- according to the specific risks of the product and the manufacturing process."	M
2.3.2	255-257	It is not clear why process validation should not be essential for investigational medicinal products. We believe that process validation is essential also for investigational medicinal products. Consider revising.	**In the text:** "Replacement of routine batch testing by process validation. *While process validation is usually not required for investigational medicinal products, it may be very important when routine in-process or release testing is limited or not possible.*" **Proposed change:** "Replacement of routine batch testing by process validation. *Process validation can replace routine batch testing when routine in-process or release testing is limited or not possible. However, whenever possible, it is strongly recommended to perform process validation for any kind of ATMP product.*"	M
2.3.2	265-267	Unclear.	**In the text:** "If the results of the sterility test of the product are not available at release, appropriate mitigation measures should be implemented, *including information of the treating physician.*" **Proposed change:** "If the results of the sterility test of the product are not available at release, appropriate mitigation measures should be implemented, *including provision of information to the treating physician.*"	M
2.3.3	275-313	ATMPs are subjected to substantial manipulation by definition.	Consider substitution of the definition *'ATMPs which are not subjected to substantial manipulation'* with *'cellular products'* through all the paragraph.	M

3.2	366	Adequate training of specialised personnel is crucial to ensure that standard procedures are properly applied. For this reason, in order to ensure quality and safety of the final product, the training programmes must be thoroughly documented.	**In the text:** "*Record of training should be kept.*" **Proposed change:** "*Training programme must be tracked and documented according to an appropriate SOP, belonging to the quality system.*"	M
2.3.3 *2.3.44.* *2.2* *17.4*	299-302 322-327 516-519 2174-2179	Incoherence among different sections. Please revise and clarify.	**In the text** **299-302:** "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 clean area of grade D." **322-327:** "For first-in-man clinical trials, production in an open environment may be performed in a critical clean area of grade A in a background clean area of grade C if appropriate controls of microbiological contamination, separation of processing procedures, and validated cleaning and disinfection are put in place. A risk-analysis study should be conducted and it should be demonstrated that the implemented control measures are adequate to ensure aseptic manufacturing." **516-519:** "Production in an open system: In general, when the product is exposed to the environment (e.g. working under laminar air flow), a critical clean area of grade A with a background clean area of grade B (or similarly controlled environment) is required." **2174-2179:** "If justified having regard to the risks and provided that the approach is supported by validation data (e.g. leak testing and pressure check of the equipment), a controlled but non-classified background environment could be acceptable if the time between the donation and administration of the material is very short and the manufacturing is performed at the operating room in the hospital (the patient is also in the operating room waiting for administration of the ATMP)."	H
3.4	430-432	Quality assurance (QA) cannot rely upon the same person as quality control and production, not even in a small organisation. In such a case, how would you define small organisations? Please, consider the proposed change.	**In the text:**"*In small organisations, where teams are multi-skilled and trained in both QC and production activities, it is acceptable* that the same person is responsible for *both roles (production and quality control)* with respect to different batches." **Proposed change:** "*During development, is permissible* that the same person is responsible for *both roles (production and quality control)* with respect to different batches."	H
4.2.1	468-469	Materials from infected donors should be segregated, but what would be the infectious agents to consider to satisfy this requirement? Which one the criteria to decide which agents to screen for and which not?	**In the text:** "Specifically, manufacturing activities involving infectious viral vectors (e.g. oncolytic viruses) or materials from infected donors should be done in a segregated area." **Please clarify if this implies the need for infectious agent testing of all starting cell material (autologous and allogeneic).**	H

4.2.2	495-496	All the ATMPs for the nature of the final product defined as such cannot undergo sterilisation processes.	**In the text:** "Special attention should be paid *to products for which there is no sterilisation of the finished product.*" **Proposed change:** "Special attention should be paid *to the specific risks of the products and the manufacturing process especially because, at the present time, no ATMP can undergo the sterilisation of the final product.*"	L
4.2.2	533-537	Where disinfectants are used, the cleaning regimen should also ensure that residual cleaning agents/disinfectant are sufficiently removed to minimize product contamination.	**In the text:** "Appropriate cleaning/sanitation of clean areas is essential. Fumigation may be useful to reduce microbiological contamination in inaccessible places. Where disinfectants are used, it is advisable that more than one type is used to avoid the development of resistant strains." **Proposed change:** "Appropriate cleaning/sanitation of clean areas is essential. Fumigation may be useful to reduce microbiological contamination in inaccessible places. Where disinfectants are used, it is advisable that more than one type is used to avoid the development of resistant strains*. Efficacy and safety of the cleaning procedures should also be ensured through an appropriate process validation.*"	M
4.2.3	583-585	To ensure the safety and the quality of the final product, it is important that the measures and procedures to be enacted in case of these events are decided and communicated beforehand. In the occurrence, their execution must be documented.	**In the text:** "Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation." **Proposed change:** "Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation. *A detailed programme including appropriate corrective measures should be applied and documented, according to a SOP protocol set beforehand.*"	H
6.2	787-791	Given the evolution/refinement of the manufacturing and quality control processes, being able to retrieve the characteristics of each batch is essential also for the investigational ATMPs. However, also the quality of each batch is an essential piece of information which should be tested and documented for each batch.	**In the text:** "Given the evolution/refinement of the manufacturing process and quality controls that is typical of investigational products, it is important that the level of documentation is sufficient to enable the identification of specific characteristic of each batch." **Proposed change:** "Given the evolution/refinement of the manufacturing process and quality controls that is typical of investigational products, it is important that the level of documentation is sufficient to enable the identification of specific characteristic and *proved quality* of each batch."	M

6.5	865-870	Retention times for documentation appear not to be adequate to the context of ATMPs.	**In the text:** "Batch documentation (i.e. documents in the batch processing record, results of release testing, as well as -where applicable- any data on product related deviations) *should be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the QP, whichever is the longest. For investigational medicinal products, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used.*" **Proposed change:** "Batch documentation (i.e. documents in the batch processing record, results of release testing, as well as -where applicable- any data on product related deviations) *should be kept indefinitely, whether the product was used for treatment or for investigational purposes.*"	H
7.3	996-999	Audits for blood centres supervised under the applicable regulations are not required according to this section, but what about other agreements, such as the mutual recognition framework? Are those sufficient to accept a product without any further audits by manufacturers? This must be explicitly stated.	**In the text:** "Blood establishments and tissue establishments authorised and supervised under Directive 2002/98 or Directive 2004/23 997 do not require additional audits by the ATMP manufacturer *regarding compliance with the requirements on donation, procurement and testing.*" **Proposed change:** "Blood establishments and tissue establishments authorised and supervised under Directive 2002/98 or Directive 2004/23 997 do not require additional audits by the ATMP manufacturer*, unless a different intended use is foreseen.*"	H
8	1075-1076	ATMP/viral banks/seed lots should not have different minimum requirements.	**Recommend to refer to existing cell bank regulations for environmental requirements.**	M
9.1	1159-1162	In order to ensure quality and safety of the final product, it is important to correct any deviation from standard procedures as far as possible.	**Clarify better roles and responsibilities of the different professional figures in this case.**	
9.5.1	1271-1274	Typo (line 1272).	**In the text:** "Likewise, it is acceptable to conduct a manufacturing activity in a clean room which hosts an *incubator* which is used for a different batch/product if there is separated expulsion of exhausted air from the isolator and regular integrity checks of the isolator." **Correction:** "Likewise, it is acceptable to conduct a manufacturing activity in a clean room which hosts an *isolator* which is used for a different batch/product if there is separated expulsion of exhausted air from the isolator and regular integrity checks of the isolator."	M
9.5.2	1326-1328	Typo (line 1326).	**In the text:** "The integrity of the *sterilised filter* should be verified before use and should also be confirmed after use by an appropriate method (e.g. bubble point, diffusive flow or pressure hold test)." **Correction:** "The integrity of the *sterilising* filter should be verified before use and should also be confirmed after use by an appropriate method (e.g. bubble point, diffusive flow or pressure hold test)."	L

11.2	1674-1683	Import testing for batch release of ATMPs should be the exception. Because of the peculiar characteristics of the products, qualitative and quantitative analyses are likely to be impossible. It would be useful to establish a mechanism to accept the testing performed in the country of origin. It is also essential to check the coherence between this passage and the GMP requirements.	**Clarify the regulatory framework and verify alignment and coherence with GMP and mutual recognition framework requirements for manufacturers.**	H
12.1	1836-1838	This sentence seems to require an identity test for each batch to match product to patient (starting material to recipient).	**In the text:** "In case of autologous products or donor-match situation, a *control should be carried out to verify* the match between the origin of the starting material and the recipient." **Proposed change:** "In case of autologous products or donor-match situation, a *traceability control system should be in place to ensure* match between the origin of the starting material and the recipient *by documentation lab review.*"	H
12.2.2	1864-1865	In the case of ATMPs the likelihood to be able to retain part of the sample is very low. Alternative strategies should be sought, in order to ensure the safety in the chain of identity, but also the timely delivery of the treatment to the patient.	**In the text:** "*Samples are generally retained for analytical purposes should the need arise during the shelf life of the batch concerned (reference samples) and for identification purposes (retention samples of a fully packaged unit from a batch of finished product).*" **Suggested change:** "*Due to the nature of ATMPs is unlikely that retention samples of the finished products can be kept, therefore, an alternative strategy for retention sampling should be justified and documented.*"	H
12.3	1958-1970	Method transfer is described only.	**Proposal to include additional paragraph for outsourcing of the manufacturing process to another site or transfer to another manufacturing site.**	H
15	2054-2073	This topic is covered by the applicable EU GMO guidelines	Suggest to cross-reference appropriate guideline (EC2001/18 Directive, CHMP/GTWP/125491/06 and EMEA/CHMP/473191/06).	H
		List of abbreviations is missing	**Consider insertion.**	M