Consultation Document
Good Manufacturing Practice for Advanced Therapy Medicinal Products
28 June 2016

1. General Comments:

- The guidance document represents a distillation of the GMP principles outlined in Eudralex volume IV and is in line with AZ/MedImmune's current understanding of EU/FDA expectations. As written, it will present few issues for AZ/MedImmune.

  It is recommended that some instruction be included within the document describing the relationship between this guidance and Eudralex volume IV, especially when differences occur.

2. Specific Comments on Text:

Section	Page or line number	Comment and rationale; proposed changes (if any)
Table of contents,	1	Table of contents. Suggest adding a glossary of terms and, where relevant, include reference to the source document for the definitions (e.g. of an ATMP, PAT for example).
1	101	The relationship to Eudralex volume IV should be stated – is this guide to be used in conjunction with Volume IV or to replace it? A clear statement should be included to indicate which GMPs take precedence in the light of any differences between the two guidelines.
2.2	199-205	This section discusses the importance of the quality system but no further guidance is then provided. Consider adding guidance similar to that in Chapter 1 of Eudralex volume IV part I.

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2.2	206-208	*"The description of the manufacturing process and process controls in the clinical trial authorisation application should also describe, as appropriate, the quality strategy of the manufacturer when the risk-based approach is applied."* The term quality strategy needs to be expanded to be more proscriptive as this could be misinterpreted. It is suggested to add the following text*:"The Quality Strategy should include for example: the manufacturer's approach to assuring sterility of the product, in-process testing strategies for assuring product quality as well as other process-specific controls in place to mitigate identified risks"*
2.3	236	Clarify that the risk referred to in this line is risk to patient. *"Additionally, it is important to take into account the potential level of risk to the patient of the raw material due to the intrinsic properties thereof (e.g. basic media vs. growth factors), or the use thereof in the manufacturing process (higher risk if the raw material is in direct contact with the starting materials)."*
2.3	293-295	Reword: "*It is stressed that it is the responsibility of the manufacturer to ensure that the manufacturing of ATMPs is done under aseptic conditions, also when the manufacturing process does not involve substantial manipulation"* Proposed change: *"It is stressed that it is the responsibility of the manufacturer to ensure that the manufacturing of ATMPs is done under aseptic conditions even when the manufacturing process does not involve substantial manipulation."*

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2.3.3	311	Change: *"QP release is an essential requirement applicable to all medicinal products*" Proposed change: *"QP certification is an essential requirement applicable to all medicinal products"*
3.3	396-397	Move the line: "*For every worker in a grade A/B area, clean (sterilised) protective garments should be provided at each work session.*" To the section specifically for Grade A/B (lines 387-394) to make the requirement more obvious.
4.2	468-471	The section: "*Specifically, manufacturing activities involving infectious viral vectors (e.g. oncolytic viruses) or materials from infected donors should be done in a segregated area. The arrangements for the segregation of the area should be demonstrated to be effective.*" Proposed change: It is suggested to add wording to make it clear that this is not an exhaustive list of examples of manufacture requiring a segregated area.

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4.2.2	520-526	The section needs to be reworded. What are listed as considerations are actually examples where open systems can be justified. What would be more helpful is to include these as examples but to list the points to consider when deciding if open processing can be justified. Proposed change: "*In the case of production in an open system, It is possible to justify a background of Grade C where there are further microbial contamination controls downstream of the step. For example:- Preparation of solutions which are to be sterile filtered during the process canbe done in a grade C environment.- For the manufacturing process of viral vectors, two steps should be considered:* *o The expansion phase before the sterilizing filtration can be performed in a critical clean area of grade A with a background clean area of grade C.* o *The sterilizing filtration and filling need to be performed in a critical clean room of grade A with a background clean room of grade B."*
4.2.2	527-604	Annex 1 is soon to be updated. Where variations between this guidance and annex 1 occur, which will take precedence? This should be stated or the detail deleted and reference made to Annex 1 of Eudralex vol IV part I.
4.2.3	580-585	Is this in line with current thinking with regards to the revision of Annex 1 where removal of monitoring of 5um particles has been suggested?

General Principles	650-667	Row 660 States "*Aseptic connections should be performed in a critical clean area of Grade A with a background clean area of Grade B*". AZ use some single use sterile connectors that are designed to be made in lower grade areas for completely closed systems e.g. Pall Kleenpak and Millipore Lynx S2S. These are used widely within AZ & AZB and connections made in background rooms. It is requested that this statement be clarified to say *"validated processes for sterile connections may be employed in lower grade areas".* This may impact RAB systems as connections can be made outside the RAB with single use systems.
5.1	656-658	The section is discussing equipment but this paragraph is about components. Please clarify what is meant by components in this section, for example are the components referred to parts of the equipment or product container and closures).
5.2	683-684	The statement "*When repair or cleaning operations occur in a clean area, production should not be restarted until it has been verified that the area has been adequately cleaned*" needs to be expanded to add the requirement to ensure the required environmental standard has been re-established. Proposed change: *"When repair or cleaning operations occur in a clean area, production should not be restarted until it has been verified that the area has been adequately cleaned and the required environmental standard has been re-established."*

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6.2	724-730	Minor correction to the section suggested: *"Rationales for changes should be recorded and the consequences of a change on product quality, safety or efficacy and, where applicable, on any on-going non-clinical study or clinical trials should be investigated and documented. It should be noted that changes into the manufacturing requirements approved as part of the marketing authorisation must be submitted to the competent authorities (variation procedure), and that substantial modifications in the manufacturing process of an investigational ATMP require approval by the competent authorities."*
6.2	781-782	*"It is recalled that, for authorised ATMPs, the identification code received from the tissue establishment/blood establishment"* *Proposed change:* *"It should be noted that for authorised ATMPs, the identification code received from the tissue establishment/blood establishment"*
6.2	786-799	The information listed as required to be in the Product Specification File is incomplete when compared to Annex 13 of Eudralex volume IV, part I.: Proposed change: Either align the section with section 9 of Annex 13 or refer to the section for full details.
6.2	807-809	The line: "*Where different manufacturing steps are carried out at different locations under the responsibility of different QPs, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.*" appears to be in the wrong place. Proposed change: It is suggested to move this to the earlier section discussing PSFs.

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6.3	809-840	Line 809 states, with regards to record retention: "*As a minimum, the following should be documented*:" However the list that follows is incomplete. Significant items that are missing include: - For material receipt a check on condition upon receipt - For batch records, line clearance checks - Maintenance and calibration records for critical equipment - Training records. It is suggested that this list be either deleted, expanded or qualified as being examples as, in its current state, it is misleading.
6.6	880	The title of the section is misleading. If it truly is about traceability then this section should be moved to section 7. However if the section relates to the retention of cell/tissue data to ensure traceability then the title should be changed to reflect this.
7.1	916-929	A section on the benefits/need to qualify suppliers should be added to this section in line with industry best practice.
7	915-1068	Early stage processes for Ph I/II studies often use materials available from single sources such as T-cell activation agents. These can risk commercializability of therapy from sourcing, licensing and cost of manufacturability aspects. Recommended change: Suggest adding guidelines indicating a feasible path to changing such materials based on risk assessment and analytical characterization data of relevant intermediates to help bring the best quality products to patients.

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7	915-1068	Rapid developments are being made to improve safety profile and production processes of viral vectors used to transfer gene of interest to patient cells. E.g. Ph I/II may utilize lentivirus produced in serum containing adherant process using a low productivity based cell line. Recommended change: Suggest adding guidelines indicating feasible paths to absorbing improvements in the production of such starting materials (e.g. alter MOI to changes in process and cell line used for generating lentivirus) to facilitate the taking of the best and most cost effective product to the patient.
7.1	927	Recommend adding "*antibiotics or antimicrobials*" to statement on interference with sterility test.
7.2	960-964	It is recommended that the following statement be added: "*Where this is a potential mycoplasma contamination risk associated with a raw material, 0/.1um filtration of the material prior to use should be considered as risk mitigation step*."
7.3	1097-1100	The section should be expanded to make this more generic and introduce the need for continuous monitoring where relevant. Suggested change: "*Storage containers should be sealed, clearly labelled and kept at an appropriate temperature. A stock inventory must be kept. The storage temperature should be continuously recorded and monitored, including appropriate alarm systems such as 24/7 remote alarm systems. Other parameters necessary to ensure safe storage may also require monitoring. For example, where used, liquid nitrogen level should be monitored. Deviation from set limits and corrective and preventive action taken should be recorded."*

9.1	1159-1162	The need to investigate deviations to identify the root cause and then implement CAPAs as necessary should be added to this section. Proposed change: *"Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by the person responsible for manufacturing, with the involvement of the person/department responsible for quality control when appropriate. Deviations should be investigated in an attempt to identify the root cause and then implement CAPAs as necessary."*
9.3.1	1193-1202	Reference to the relevant pharmacopoeia standards for testing should be made in this section as should the need to have the system appropriately designed and qualified to avoid microbial contamination.
9.3.3	1208-1210	Reference to the relevant pharmacopoeial sections (testing to WFI standards) should be made in this section
9.5.1	1268-1271	The statement: "*Thus, the use of more than one isolator (or other closed systems) in the same room at the same time is acceptable, provided that there is separated expulsion of the exhausted air from the isolators and regular integrity checks of the isolator*" should be expanded to include other caveats than just those listed. Proposed change: *"Thus, the use of more than one isolator (or other closed systems) in the same room at the same time is acceptable, provided that the systems have been assessed as closed systems and any risk of cross-contamination is mitigated or eliminated. Specific items to note are that there is separated expulsion of the exhausted air from the isolators and regular integrity checks of the isolator."*

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9.5.3	1331-1354	The guidance on media fill should be updated to include that all potential interventions should be included in the simulations and "worst case" conditions mimicked where possible. Annex 1 is to be updated with more up-to-date guidance on media fills – where instructions diverge, which guidance will take precedence? This should be indicated in this guidance document.
9.5.3	1353-1354	Suggested rewording as the current statement is ambiguous. Proposed change: *"Process simulation testing to support initial validation should be performed with three consecutive satisfactory simulation tests per shift."*
9.6	1377-1378	The re-use of matrixes should also be supported by appropriate validation data.
10.1.1	1431-1448	The qualification of sterilisers should also be highlighted alongside the current examples due to criticality.
10.1.2	1492-1493	Where site PQ is not performed the justification for this should be documented as part of the validation plan.
10.1.12c	1498-1499	It should also be highlighted that ultimately it is the manufacturer's responsibility to ensure that the equipment is fit for purpose.
10.2	1505-1509	The section mentions that cleaning validation must be against predefined acceptance criteria. Guidance on how to set these criteria would be helpful. Proposed change: Suggest adding *"The justification for the selected limits should be documented in a risk assessment which includes all the supporting references. Limits should be established for the removal of any cleaning agents used."*
10.2 (ii)	1530-1534	The section should also mention that sampling (swabbing) should be at locations identified as "worst case".

10.3	1564	Reword to indicate that this is the minimum requirement. Proposed change: *"The following, at a minimum, should also be specified in the protocol:"*
10.3	1614	Explain PAT (or add to glossary)
10.3	1616-1618	Add that this (retrospective validation may be justified in the specific cases listed. Proposed change: *"Retrospective validation may be justified where time to manufacture, batch size, or other factors make prospective validation unethical (e.g. performing a biopsy only for validation purposes) or disproportionate having regard to the anticipated benefits for patients."*
10.3	1619-1622	Reword the section Proposed change: *"Process validation for a class of products: where the same manufacturing process is used for a class of products (i.e. autologous T-cell based ATMPs), the validation of the process does not need to be repeated for each of the products, in so far as the manufacturing process has been assessed and no significant differences noted."*
10.4	1364	Other assays must be demonstrably fit for purpose either by limited qualification or taking into account controls in place within the assay.
11.2	1670-1673	The QP also has to certify investigational ATMPs against the PSF. This should be added to this section.
11.5	1808-1817	This seems in direct contradiction to 11.4 and Annex 16. Additional guidance needed for the role of the QP in this scenario.

21.1	1822-1823	The statement: "*Quality control is not confined to laboratory operations, but must be involved in all decisions which may affect the quality of the product.*" is ambiguous and appears to broaden QC's role to much wider than indicated in EudraLex volume IV. This needs to be deleted or qualified. It also appears to be mixed up with the role of Quality Assurance which is not discussed within the guidance.
12.1 (vii)	1844	Should this be limited to laboratory and/or testing qualification and validation, not all such activities?
12.1(viii)	1845	This implies QC are responsible for labelling product and therefore does not align with current industry practice. Please provide clarification.
12.2.2.1	1862-1916	The section does not allow for specific requirements of investigational ATMPs as documented in Annex 13 (Eudralex vol IV part I) Proposed change: Add "*Reference and retention samples of investigational medicinal product, including blinded product should be kept for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer.*"
14.2	2064-2053	The section on recall is incomplete and does not currently meet minimum expectations of regulatory authorities. Recommended change: The following requirements should be added: • The need for periodic testing of the recall process • The need to contact the relevant competent authorities, as required by national laws) • The need for appropriate segregation • The section should be checked against the new requirements of chapter 8 of Eudralex volume IV, part I.

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