Consultation Document
Good Manufacturing Practice for Advanced Therapy Medicinal Products

MolMed comments to the DG SANTE consultation on GMPs for ATMPs pursuant to Article 5 of Regulation 1394/2007.
MolMed SpA is a medical biotechnology company focused on research, development and clinical validation of innovative therapies to treat cancer, and it falls within the EU definition of a small and medium-sized enterprise.

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Section 2. GMPs for ATMPs: general principles

Q1: Are the principles laid down in Section 2 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?). Please provide comments on the text below as appropriate.

Lines 118 – 122 seem to introduce the principle that academia and hospital institutions may adopt a quality system different from GMP. The statement "acceptable level of quality" shall be better defined and exemplified especially considering the acknowledgment that "additional flexibility is warranted". Otherwise, the overall understanding is that "lower" quality standard than GMP can be in force for production. In this case, area of derogation from GMP shall be clearly identified and justified and it should be also defined when GMP will have to be introduced in clinical development ("early phases of clinical trials" seems too generic encompassing both first-in-man and Phase I/II studies) and if this will be valid regardless the applicant (industry and pubic institution). It is worthwhile to mention that additional flexibility of quality standards will possibly turn out in a competitive advantage for those applicants still not GMP certified vs those already in compliance with the currently compulsory quality standards.

Q2: Do you consider it useful that additional level of detail regarding the application of the risk-based approach is provided in the Guideline? In the affirmative, please provide examples.

The risk based approach is absolutely important not only because the manufacturing processes are complex but also because the medicinal products could be released for infusion before the completion of all quality control tests. In these situations, the risk-based approach represents the tool used by the QP to identify the potential risks for the release and decide accordingly.

Q3: How should the quality systems established in accordance with Directive 2004/23[2] be recognised in terms of GMP compliance for products that are ATMPs solely because the use of the relevant cells/tissues is for a different essential function in the recipient as in the donor (i.e. the manufacturing process does not involve any substantial manipulation)? What about the JACIE accreditation system?

A non substantial manipulation by definition leads to an non-medicinal product and this is generally associated with a same function of cells before and after manipulation (or in the donor and in the recipient). The functional difference in recipient and donor (or pre/ post manipulation) is one of the main criteria adopted for the ATMP definition (see Annex II). The risk-based approach above mentioned should be applied in this case, rather than adopt different accreditation systems, such as JACIE.

Section 3. Personnel

Q4: Are the requirements laid down in Section 3 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?). Please provide comments on the text below as appropriate

It should be emphasize the importance of personnel scientific knowledge of the product.
In addition, there are not included any specific requirements related to qualification of operators in terms of aseptic manipulations

As an ATMP may be in itself a GMO or contains a GMO, it might be worthwhile to refer to specific GMO guidelines or mentioning specific protective measures for GMO handling, when mentioning protective garments (lines 138-139).

Section 4. Premises

Q5: Are the requirements laid down in Section 4 sufficiently well-adapted to the specific characteristics of ATMPs? Please provide comments on the text below as appropriate.

It should be emphasize the importance of environment conditions control to assure the welfare of the operators to reduce as much as possible the risk of contamination (4.2 Production areas)

Lines 212-214 should be clarified. The attention should not be paid to the filling process only, but to all the aseptic manufacturing process in the case, for example, of medicinal products manufacturing processes performed all in aseptic conditions.
The premises needed to be fully validated not only for commercial production because the safety of the product needs to be ensured also for clinical trials (line 214).
Lines from 220 to 223 are not related to aseptic process.

Q6: Do you consider that there are additional flexibilities that could be applied in connection with the requirements related to premises without compromising the quality of the ATMPs manufactured for commercial purposes?

Q7: Do you consider that there are additional flexibilities that could be applied in connection with the requirements related to premises without compromising the quality of investigational ATMPs? If appropriate, please consider possible differences between first-in-man clinical trials and pivotal clinical trials.

Q8: Should the use of a clean room with an A grade with a background of C or D grade be allowed for early phases of clinical trials (with the exception of gene therapy investigational medicinal products), provided that the specific risks are adequately controlled through the implementation of appropriate measures? Please substantiate your response. In particular, if you consider this option

should be introduced, please address the benefits of introducing such flexibility and explain what measures could, in your view, be applied to avoid cross-contamination having regard to the potential risks (e.g. the level of cell manipulation, the use of processes that provide extraneous microbial contaminants the opportunity to grow, the ability of the product to withstand purification techniques designed to inactivate or remove adventitious viral contaminants, etc.)

Grade B surrounding is required for aseptic productions, both for clinical trials (at any development stage) and commercial production (reference to EU-GMP Guideline Annex 1 should be included).

Grade B surrounding could not be required for the manufacturing process of cell banks if the following assumptions are applicable:

- *the MCB is the starting material of the WCB;*
- *the WCB is in turn the starting material of a viral vector that is classified as a starting material for the manufacturing of the medicinal product;*
- *microbiological In Process Controls are foreseen during the cell banks manufacturing processes;*
- *bioburden tests are performed during viral vector production manufactured from the WCB;*
- *Viral vectors manufactured from WCB are finally sterilizing filtered.*

Regarding the manufacturing process of viral vectors, two steps should be considered:

- *Expansion phase before the sterilizing filtration that could be performed in Grade A with Grade C surrounding because low bioburden process*
- *Sterilizing filtration and filling that need to be performed in Grade A with Grade B surrounding because aseptic process*

Consistently, it is not clear why GTMP (e.g. manufacture of ex vivo genetically modified cells) shall be excluded from the measure, considering that the primary aim of a suitable production environment is to minimize the risk of contamination of the cells (regardless that these are genetically modified or not) during manufacture.

Section 5. Equipment

Q9: Are the requirements laid down in Section 5 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate

Lines 283-284: the expectations should be better clarified. Is it related to the performance of CCIT?

Lines 291-292 it is not appropriate to include computer because the computer systems do not require periodical requalification, checks calibration, etc. The computer systems need to be managed in accordance to Annex 11 and GAMP

Section 6. Documentation

Q10: Are the requirements laid down in Section 6 sufficiently well-adapted to the specific characteristics of ATMPs? Please provide comments on the text below as appropriate.

Lines 305 – 306: two primary types of documentation are mentioned. This is not completely correct since it is needed to maintain the pyramid structure starting from the policies, then SOPs, working instructions and quality data.

Line 313: SMF is not required only for commercial manufacturing, but also for clinical trial productions.

Line 337: the manufacturer may rely on the certificate of analysis not only for Investigational ATMP, but also for commercial productions, considering the complexity and the cost of same raw materials. An evaluation could be done on the basis of a risk assessment.

Line 336: storage and transport conditions and precautions should be considered also for raw materials.

Q11: Do you consider that there are additional flexibilities that could be applied –without compromising the robustness of the quality system- in connection with the documentation obligations for ATMPs manufactured for commercial purposes?

Q12: Do you consider that there are additional flexibilities that could be applied –without compromising the robustness of the quality system- in connection with the documentation obligations for investigational ATMPs? If appropriate, please consider possible differences between first-in-man clinical trials and pivotal clinical trials.

Section 7. Starting and raw materials

Q13: Are the requirements laid down in Section 7 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.

Human tissues and cells used as starting materials or raw materials should be in accordance to tissues/cells directives but some disharmony is present at member state level.

Moreover, viral and microbiological testing requirements to allow the introduction of a human biological material in the GMP Manufacturing area and QC area are not described. This point needs to be regulated.

Line 450: some suggestions should be provided about quality and safety requirements when plasma derived materials marketed for human use (i.e human albumin, human serum) are used as components of culture medium during ATMPs manufacturing or excipient.

Section 8. Seed lot and cell bank system

Q14: Are the requirements laid down in Section 8 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.

Establishment and testing of seed lot and cell bank systems is an already well established procedure for production of rDNA molecules. It is not deemed that production of retroviral vector introduces critical differences in this step, therefore the already in use guideline with the proposed text provides a sufficiently well defined frame for the applicant. The only room of flexibility would be in documenting the origin of the cell line which might be in some case critical. It is recognized, however, that a non well documented cell history might have safety implications.

Section 9. Production

Q15: Are the requirements laid down in Section 9 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

Point 9.5 – Packaging materials: A step-wise approach in demonstrating compatibility of the primary packaging is advisable (and indeed already in force in practice), especially considering that most of the materials currently used for packaging ATMP products are already adopted for cell packaging in standard clinical use. It could be reasonable to include complete data package for compatibility for commercial applications and in case of large Phase III studies, whilst limited data can be required for first-in-man and Phase I/II studies.

It should be clarified the requirement to perform the CCIT, considering the different stages of development.

Section 10. Qualification and validation

Q16: Are the general principles laid down in Section 10 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

Line 715: it is reported that validation of aseptic processing should include a process simulation test. This needs to be discussed because if this means that the performance of one run is enough this is not appropriate.
Line 723 and 724: it should be clarified the meaning of "significant changes should be validated", considering that it has been stated above (line 711) that for clinical trials manufacturing process a validation exercise could be not applicable.

Q17: Due to the biological variability inherent in ATMPs and limited batch sizes, process validation is particularly challenging for ATMPs. A pragmatic approach as to the specific requirements on validation should be developed. Please provide suggestions.

Section 11. Qualified person and batch release

Q18: Are the requirements laid down in Section 11 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

Lines 870-873: in addition to the procedure for out of specification test results obtained after the release of the product (products infused prior the final release) a procedure should be in place for the use of products in which OOS are obtained before release for infusion, considering the ethical issues specifically associated to ATMPs. Should clinical evaluation of risk/benefit support the release of the batch for infusion in the presence of an OOS? More details should be given on this subject, in particular for commercial ATMPs.

Lines 883-885: it should be clarified how can be managed the notification to the competent authority of a significant deviation and the release of the batch in the case of ATMPs with a shelf life of few hours.

Section 12. Quality control

Q19: Are the requirements laid down in Section 12 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

Lines 931-932: it should be considered that not only for biological starting materials but also for the medicinal product it is not possible to store reference/retention samples according to EU GMP guidelines annex 19 and annex 13. Some indications should be given about the specific purpose of the reference samples storage for ATMPs that have to be feasible considering the nature of the product. Storage of medicinal product retention sample is often not applicable.
Line 940: commercial ATMPs should also be considered.
Lines 938-949: some indications should be given also for the storage period of samples of medicinal products; indications and for the storage of reference and retention samples for commercial ATMPs.

Point 12.3 – testing: some analytical tests might be difficult to be "one shot" validated because of the intrinsic variability of the biological material. Therefore, a stepwise approach could be considered for analytical assay validation, designing a general strategy that defines minimum requirements for first-in-man applications (thus providing a higher degree of flexibility). Of note, even though never formalized in a regulatory guideline, such stepwise approach has been so far adopted in practice (i.e. safety and microbial assay validated before first-in-man, potency and characterization assays validated throughout clinical development, with full validation required only before commercial use).

Section 13. Outsourced activities

Q20: Are the requirements laid down in Section 13 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

Section 14. Quality defects and product recalls

Q21: Are the requirements laid down in Section 14 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

Section 16. Reconstitution of product after batch release

Prior to administration to patients, ATMPs may require certain additional steps after they have been released by the QP of the manufacturer. These steps are generally known as "reconstitution". Examples of reconstitution include thawing, dissolving or dispersing the ATMP, diluting or mixing the ATMP with the patient's own cells and/or other substances added for the purposes of administration (including matrixes). Reconstitution is typically conducted in a hospital.

Q22: Do you agree with the principle 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?

It should be clarified what means "validation". Our position is to perform appropriate studies in order to demonstrate that this reconstitution step has no impact on product quality.

Q23: Do you agree with the principle that reconstitution is not manufacturing and therefore is outside GMP?

We agree.

Q24: What activities should, in your view, be considered as reconstitution?

Reconstitution activities allowed could be referred to the principles of non-substantial manipulations.
Reconstitution could be for example a dilution of the product before infusion.
It should discuss situations that require more steps of manipulations, i.e thawing, centrifugation (to discard cryopreserving agents, i.e DMSO) and resuspension in infusion buffer, and assess if they can be considered as substantial or not substantial manipulations.

Section 17. Automated production of ATMPs

Devices that permit the selection and/or manipulation of cells are emerging. Often these devices are intended to be used in hospitals. The automated production of ATMPs through these devices poses specific challenges.

Q25: How do you think that the GMP obligations should be adapted to the manufacture of ATMPs through the use of automated devices/systems? Who should be responsible for the quality thereof?