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European Commission Consultation Document: GMP for ATMPs

By e-mail to SANTE-D5-ADVANCED-THERAPIES@ec.europa.eu

Introduction:

For the past two years I have been the co-ordinator of an EU FP7 funded project, AGORA (**ADVANCED THERAPY MEDICINAL PRODUCT GOOD MANUFACTURING PRACTICE OPEN ACCESS RESEARCH ALLIANCE**). This is a consortium of GMP practitioners involved in the manufacture of ATMPs and receives support from the European Union's FP7 Research Programme. AGORA performs a series of specific actions to address current unmet needs and critical issues arising from our previous FP7 Academic Good Manufacturing Practice (GMP) study on the development and delivery of new advanced therapies for the treatment of cancers and regenerative medicine.

Recent EC actions have attempted to ensure the development, provision and free movement of ATMPs within the EU. However, we found substantial heterogeneity in the regulatory practice across member states which is leading to confusion and uncertainty, creating a severe barrier to development and delivery of these novel medicines which was weakening the position of EU academics and industry to collaborate and compete globally in this expanding field.

The outcome of the current impact assessment by "Academic GMP" concluded that a framework of support and training was needed to facilitate the implementation. AGORA contributes to this framework through the establishment of a technology transfer network, training programmes, an interactive web-site, representation and provision of information on pathways, regulations, technologies and resources across the European Union.

This response to the consultation exercise is personal and not formally from the "AGORA Consortium" but it reflects the opinions from most of the consortium partners collected over the past 2 years.

General Comments

It is difficult to understand the extent to which the outcome of this Consultation and whether it will serve to highlight issues of specific importance for ATMPs or, instead, provide additional specific guidelines or even regulatory changes for this innovative group of medicines. A contentious issue over the past 6 years of ATMP developments in the EU has been the clean room classes required for the manufacture of ATMPs and it is interesting that this has been identified in this document too. However, the current legislation in annex II of the EU GMP Guideline already allows a risk-based approach to all aspects of GMP manufacture and most of our academic GMP colleagues believe that this is sufficient to justify a clean room environment that differs from Annex I of the GMP Guideline on a case by case-basis. Many of us, which represent a broad experience of ATMP manufacture in academic settings in multiple EU member states, do not support the *de facto* reduction in the environmental standards of the manufacturing for ATMPs in early phase trials

as suggested. Part of the unique nature of ATMPs is the paucity of appropriate and informative pre-clinical models so the true risk profile is impossible to determine until the first-in-man study. This raises two important ethical considerations:

1. Early phase trials will involve untested therapies in very small batch sizes and with very few process development and process validation runs prior to the first clinical manufacture. This is compounded by the relative difficulty in sourcing appropriate human donor material to conduct multiple process validation runs. It is therefore difficult to accept that the aseptic manufacturing procedures can have been adequately tested in pre-clinical development to allow manufacture at a grade below “A in a B” background. Plainly, where sufficient data do exist to support a lower standard then this can be addressed in the “risk based approach” already within Annex II.
2. It remains a fact that most ATMP development in the EU remains in academic settings. The emphasis of academic trialists is largely enquiry driven and is rarely focused on drug development. There remains a somewhat naïve belief in many academic centres that a small phase I-II trial which produces interesting results will lead to a commercial take-up and thus commercial development. The bald truth is that this is rarely (never?) the case. Pharmaceutical and biopharmaceutical companies entering the space are presented with poorly designed manufacturing processes but with compelling clinical data for development of the ATMP. Where the academic manufacture of the ATMP has been naïve the time to development of a process fit for drug development is protracted and, since ATMPs are famously difficult to define adequately, an enormous task in demonstrating that the new manufacturing process delivers the same ATMP. The reduction in GMP standards for early phase trials actually *encourages* poor manufacturing processes and is likely to make the future development of a promising ATMP *more* unlikely. This is a significant ethical problem since patients being treated in first-in-man trials often express the belief that they are willing to take on the risk since it “may help other patients”. Using a poorly designed aseptic process in phase I simply because it is easy to deliver is likely to reduce the probability of commercialization or even non-commercial wide spread adoption under the HE supply route.

As a group we do not believe that erosion of GMP standards for early phase trials of ATMPs would improve the development of novel ATMPs in academic or commercial settings.

1. Specific Comments:

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.

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.

Comment to Q1 and Q2: I believe that the principles in Section 2 can be well adapted to the manufacture of ATMPs even in F-I-M applications if a suitable risk-based approach is applied. We propose to add additional details as follows: A risk-based approach is understood to form the basis for appropriate quality controls to be implemented, and for additional measures to be taken in the manufacture. Especially for ATIMPs in early phases of clinical testing, the risk assessment should include a clinical perspective as to the balance of risks and potential benefits for the intended use.

Q3: How should the quality systems established in accordance with Directive 2004/232 be recognized 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?

Comment: We must start from the premise that an ATMP is a medicinal product as defined in 2009-120-EC and thus the standards laid down in the Directive 2004/23 are not appropriate. We believe that the existing annex II offers enough opportunities to deviate from the GMP requirements if justified by a risk analysis on a case by case basis. However, the concept should be to maintain standards of GMP as laid down in Annex 2 to the GMP Guideline and justify deviations based on risk, rather than effectively opening the doors to standards outside GMP. In line with this, the JACIE standards are not seen as appropriate beyond minimally manipulated products because the risk profile of an ATMP is likely to be greater than a conventional cell therapy product. JACIE standards are certainly appropriate to define the standards for the procurement of apheresis products or similar starting materials for further processing.

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.

Comment: We suggest to add a reference to the respective ISO 14944 document to further define the details of the protective garment.

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.

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.

Quote: “It is recommended that the design of the premises permits the production to take place in areas connected in a logical order corresponding to the sequence of the operations and required level of cleanliness. Likewise, the arrangement of the working environment, and specifically of the equipment and materials, should minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination, and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.”

Comment: We would suggest that, beyond a recommendation, the design of the premises should allow the production to take place in a logical order, irrespective of the level of development.

Quote: “4.2.2. Aseptic environment:

For commercial production of ATMPs, the premises should be fully validated.”

Comment: Why should a validation of the premises be required only for the commercial production? As stated above, the greatest risk of failure of aseptic production is at phase I trial when the experience in product manufacture is least.

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?

Comment: We agree that the use of a clean room with an A grade and a background of C is conceivable and in-line with the requirements of US cGMP. However, rather than make this an appropriate standard for early phase trials and not for later phases is counter-intuitive; early phase trials where production experience and sterility data are few should require a higher level cleanroom environment. As experience increases then a risk assessment may reduce this to "A in C" for late phase trials and for commercial manufacture. This would be supported by considerable data to inform the risk assessment AND, the ability to move to a grade C environment without "closure" of the process would greatly facilitate commercialization of these products and thus wider availability to patients.

We do agreed that, for gene therapy investigational medicinal products, an A grade with background of B should be required, added by appropriate measures to ensure environmental protection.

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.)

Comment: Advantages would be that the gowning procedures for a C background would be much less cumbersome and cost-intensive than gowning to grade B. Many ATMP manufacturing processes are long and require the use of multiple pieces of equipment and the completion of long and detail manufacturing records. The physical impact on the laboratory technician/scientist of long periods in grade B gowning must be taken into account in any risk assessment of ATMP manufacture as must the cost of compliance with "A in a B background". ATMPs are and will remain expensive therapies, especially those which are patient-specific. Adding manufacturing costs for Grade B manufacture will decrease the availability of these therapies to the patient population. In the situation where it is appropriate to reduce the requirements to "A in C" (akin to US cGMP) we recommend that measures to avoid cross-contamination should include:

- documented concept of line clearance
 - production in campaigns
 - a detailed plan for the handling of the fully closed product outside A grade cleanroom areas, and
 - stringent measures for qualification of personnel: microbial control, media fill
 -
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.

Comment: Yes, the requirements laid down in Section 5 are appropriate and seen as sufficiently flexible, even forthcoming.

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.

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.

Quote: “As a minimum, the following should be documented:

(i) Written request to start manufacturing a batch (manufacturing order).

(ii) Specifications for raw materials, including:

- Instructions for sampling and testing, as appropriate. For investigational ATMPs, the manufacturer may rely on the certificate of analysis of the supplier if this is considered appropriate having due regard to the risks.”

Comment: We interpret this as follows: the supplier qualification must take the risks inherent in the respective materials into consideration, as part of an overall risk management plan for the product to be manufactured. Based on the risk perceived, auditing of the manufacturer may be necessary; in any case, the decision as to the qualification of the material and the supplier must be justified and documented.

Quote:

“- Quality requirements with acceptance criteria.

- Maximum period of storage.

- For raw materials of biological origin, the source, origin, traceability and suitability for the intended use should be described. Contracts and quality requirements agreed with third party suppliers should be kept.”

Comment: A contract may not be necessary when the qualification of the material reveals that the material is manufactured as a medicinal product, with a batch release by a Qualified Person and batch documentation in the manufacture of the respective ATMP.

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.

Quote: “The ATMP manufacturer should verify compliance of the supplier with the agreed specifications. The level of supervision and further testing by the ATMP manufacturer should be proportionate to the risks posed by the individual materials. Blood establishments and tissue establishments authorised and supervised under Directive 2002/98 or Directive 2004/23 do not require additional audits by the ATMP manufacturer regarding compliance with the requirements on donation, procurement and testing. In addition to the specifications for the starting materials, the agreement between the ATMP manufacturer and the supplier (including blood and tissue establishments) should contain clear provisions about the transfer of information regarding the starting material, in particular, on tests results performed by the supplier and traceability data.”

Comment: The availability of suitable raw materials for manufacture of many ATMPs is challenging and small GMP units are unable to thoroughly audit all critical suppliers. A requirement that all raw materials are supported by a certificate of analysis certifying that a quality standard pre-determined by the end

user has been met should be adequate for early phase trials. We very much welcome the proposal that licensed blood or tissue establishments do not need to be audited and suggest that it is expressly given that an establishment licensed in one EU member state may supply starting materials to an ATMP manufacturer in any other member state without further audit.

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.

In exceptional and justified cases, it might be possible to accept the use of cell stocks/cell banks and viral seed stocks that were generated without full GMP compliance. In these cases, the lack of GMP compliance may require additional testing to ensure proper quality of the starting material. In all cases, the overall responsibility for the quality lies with the ATMP manufacturer.

Comment: agreed.

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.

Quote: “The effects of changes in the production in relation to the quality of the finished product and consistent production (appropriate to the relevant stage of development) should be considered prior to implementation. It is recalled that changes into the manufacturing requirements approved as part of the marketing authorisation must be agreed by the competent authorities and that substantial modifications in the manufacturing process of an investigational ATMP also require approval by the competent authorities.

Critical operational (process) parameters, or other input parameters which affect product quality, need to be identified, validated/qualified (*see* Section 10), documented, and shown to be maintained within requirements. For investigational medicinal products, the identification and control strategy of critical parameters should be based on knowledge available at the time.”

Comment: agreed.

Quote: “The growth promoting properties of culture media should be demonstrated to be suitable for its intended use. If possible, media should be sterilized in situ. In-line sterilizing filters for routine addition of gases, media, acids or alkalis, anti-foaming agents, *etc.* to bioreactors should be used where possible.”

Comment: we interpret this proposal as not applicable if culture media are purchased and delivered ready to use, sterilized by the supplier, and tested by the ATMP manufacturer based on a risk assessment. Sterility tests are performed per batch.

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.

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.

Comment: We agree that qualification and validation of manufacturing processes is challenging, especially in the field of ATMPs. The proposals made in chapter 10 are gratefully acknowledged. We would like to add that, in early stages of clinical trials, a validation of quality control methods should be performed. Also, based on the ATMP in question, a validation of the manufacturing process could be performed in part prospectively (one batch, for instance), in part in parallel to the manufacturing of products intended for clinical use (two additional batches, for instance).

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.

Quote: “Safeguards to ensure that uncertified batches are not released should be in place. These safeguards may be physical (via the use of segregation and labelling) or electronic (via the use of validated computerised systems). When uncertified batches are moved from one authorised site to another the safeguards to prevent premature release should remain.”

Comment: We agree, and it should be noted that the use of a coding system could imply the coding of the product in question as:

- “released for administration”,
- “for further processing only”, or
- “not released for administration”.

Such coding systems would allow for a clear and undisputable definition of the purpose and release status of the batch.

11.4. Handling of unplanned deviations

Quote: “As long as the specifications for active substances, excipients and finished products are met, a QP may confirm compliance/certify a batch where an unexpected deviation related to the manufacturing process and/or the analytical control methods has occurred provided that:

- there is an in-depth assessment of the impact of the deviation which supports a conclusion that the occurrence does not have a negative effect on quality, safety or efficacy of the product, and
- the need for inclusion of the affected batch/ batches in the on-going stability programme has been evaluated, where appropriate.

If a significant deviation in the manufacturing process described in the clinical trial dossier has occurred, the event should be notified to the relevant competent authority if the manufacturer wants to release the product.”

Comment: agreed

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.

12.2. Sampling

Quote: “The testing strategy may be affected by the limited availability or short-shelf life of certain materials. In such cases, consideration could be given to the following options:

- Testing of intermediates or in-process controls if the relevance of the results from these tests to the intended material can be demonstrated.
- 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.”

Comment: In current practice, we do not consider process validation as a substitute for batch testing, but we welcome this proposal. In fact, this proposal bears similarities with the use of validation batches in current practice for the manufacture of blood products.

Quote: “A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained. Such events should be fully investigated and the relevant corrective and preventive actions taken to prevent recurrence.

A continuous assessment of the effectiveness of the quality assurance system is important.

Results of parameters identified as quality attribute or as critical should be trended and checked to make sure that they are consistent with each other. Any calculations should be critically examined. No trending is however required in connection with an investigational ATMP.”

Comment: agreed.

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.

Comment: agreed.

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.

Comment: agreed.

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?

Comment: agreed.

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

Comment: Current practice is different, with a manufacturing license requested in some cases for the final reconstitution. This may depend on the product in question and on the risk inherent in the reconstitution. Also, the availability of the premises needed for products of viral origin or GTMPs may not be available in all institutions, leading to local contracting of institutions in the neighbourhood and formal delivery of a finished product that, again, can be seen as a manufacturing step requiring a license. Any reconstitution which requires an analytical step (e.g. "post thaw viability testing" or "dosing of product with respect to viable cells") should be regarded as a manufacturing step and require a licence.

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

Comment: Reconstitution should be limited to adding a delivery buffer to a vial or thawing a product followed by a fixed volume dilution within one hospital or trial site, with the process taking place under the responsibility of the investigator on site.

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?

Comment: As the Point of Care Device is a Medical Device by Definition, the GMP facets addressing the resulting product are not covered by current laws and national legislation. However, products manufactured under almost entirely automatic conditions are reminiscent of "quality by design" (cf. ICH Q9), and as such may allow for a coupling of the use of the device to a standardized application for a license. The Hospital Exemption as defined in Chapter 28(2) of Regulation 1394/2007/EC might be suited for the use of PoC devices in Hospitals, unless as part of a clinical trial. The obvious challenges are in QC of the final product and in QP release. It could be possible to validate closed processes such that through closure of the process and control of the starting and raw materials the final product can be shown to fall consistently within a known range of results. In that setting it might be possible to re-interpret the QP requirements to allow automatic release on the basis of electronic confirmation that the process ran to completion without deviation.

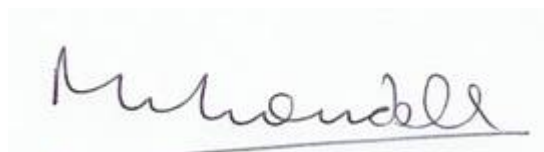
5. Conclusions

On behalf of the AGORA Consortium, we think that the European Commission Consultation Document: GMP for ATMPs incorporates many aspects that indeed would ease the adaptation of GMP requirements to the complex field of ATMPs, reflecting clinical requirements, manufacturing capacities especially in hospitals and academic institutions, and the variability inherent in the nature of these innovative products and the biological materials used. We would suggest to:

- Take the manufacturing aspects of the products supplied under the hospital exemption into consideration, which we consider as a valuable tool for many types of ATMPs manufactured in smaller scale in absence of competition with a commercially supplied alternative
- Retain the GMP-compliance of the Quality assurance, concepts of qualification and validation more thoroughly than proposed here,
- Retain the profound value of the risk-based approach as laid down in Annex 2 for biological products,
- Define the necessary premises for the manufacturing environment based on the risk assessment.

The issue of reconstitution may not be that easy to be dealt with, given the scarcity of GMP facilities available to perform this final step which, in some cases, may be defined as a manufacturing step that requires a license. This is especially important for GTMPs. As for Point of Care Devices, a hospital exemption could be used to define the interface between the Device and the product manufactured by the Device (under the premises that there is a QP, maybe employed by the manufacturer of the device?).

Thank you for providing this opportunity to comment on this valuable document.
Sincerely

A handwritten signature in black ink, appearing to read 'M Lowdell', written on a light-colored background.

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