Submission of comments on "Good Manufacturing practice for Advanced Therapy Medicinal Products"

Comments from:

Dr Aurélie Mahalatchimy, Prof Alex Faulkner and Prof Andrew Webster on behalf of the REGenableMED consortium

Please find below the answer to the 'Good Manufacturing Practice for Advanced Therapy Medicinal Products' by the REGenableMED consortium.

REGenableMED - REGenableMED is a United Kingdom Economic and Social Research Council (ESRC)-funded project (N°ES/L002779/1: http://www.york.ac.uk/satsu/regenablemed/). It brings together research team builds on work by social science experts based in Birmingham, Edinburgh, Sussex and York in the UK. It is coordinated by Pr Andrew Webster, Science and Technology Studies Unit at the University of York, UK. The project aims to examine the dynamics of innovation within the field of regenerative medicine. Using a mixed-methods social science approach, the project will undertake a detailed analysis of the interplay between business models, measures of clinical utility, patterns of regulatory oversight and clinical workflows within healthcare settings. The results of the research will inform strategies aimed at facilitating the responsible development of effective and useful regenerative medicine products and services.

All work packages of the project consider what we call the 'institutional readiness', i. e. the capacity and willingness of key pre-existing organisations and inter-organisational structures to adopt, respond to and utilise novel technologies, such as advanced therapy medicinal products as part of regenerative medicine. One work package led by Prof Alex Faulkner, Centre for Global Health Policy, School of Global Studies, University of Sussex, the UK is dealing with the role of a range of intermediary agencies, patient groups and health insurance companies, in determining what can be called 'healthcare readiness' for the field, that is, how the field aligns with and can be embedded in existing practice and how far changes need to be made. As part of this work a regular survey of regulatory tools (including relevant linked public consultations) that influence the pathways through which the field develops is performed. The draft response has been prepared by Dr Aurélie Mahalatchimy (academic lawyer) with Prof Alex Faulkner and Prof Andrew Webster (sociologists). A discussion between persons interested was then organised and the attached answer circulated to all project participants before submission.

The REGenableMED consortium is grateful to the European Commission to have been given the opportunity to contribute to this consultation.

COMMENTS & ANSWERS TO QUESTIONS

2. GMPs for ATMPs: general principles

Line 115- 116: To add the word 'to': "in comparison **to** commercial products"

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.

Line 91: It would be worth giving an example of how quality control systems are separate from production systems, since much of the rest of the document suggests that these two overlap inasmuch as production systems are also required to have formal quality control provisions in place which are not themselves about those items/practices referred to in Section 12 later in the document. Alternatively, an explicit reference here to sections 5 and 12 would be helpful. More radically, if it were possible to restructure the document such that these two dimensions could be completely separate, that would avoid uncertainties over where the boundaries between the two lie, and clarify responsibilities of different personnel. Currently 'production' can be found in various places – e.g. 4.2 and 9. Finally, it would also be worth noting that this separation is to ensure there is no conflict of interest in the processes outlined in the document.

And, in regard to the section supporting a risk-based approach, reference to 'flexibility' applies to both 'Quality control' and 'production' systems, or just the latter? If so, make this clearer.

Line 94: should some indication be given of the frequency of the 'self-inspection' process?

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.

Yes, the additional level of detail regarding the application of the risk-based approach as provided in the Guideline is useful, especially the recognition of some flexibilities for autologous ATMPs and investigational ATMPs while specifying the need to ensure the quality of the product. It would be useful to include the complete reference to the risk-based approach to facilitate navigation between guidelines.

Q3: How should the quality systems established in accordance with Directive 2004/23 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?

The JACIE system seems appropriate here.

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.

Line 141: it would be appropriate to remove 'As far as possible…' given the emphasis in this section on avoiding all possibilities of cross-contamination

4. 2 Production areas

Line 188-9: It is useful to see this paragraph dealing with multi-product facilities: there are an increasing number of publicly funded agencies providing GMP facilities to third party private companies who are competing within the cell therapy market. It would be useful to say that the design of multiproduct facilities for third party use should ensure that both the need for IP protection and quality assurance are aligned in the design of the facility.

Line 202 should read 'the lay out…'

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.

Line 438- 441: According to article 15 (1) and (4), the traceability requirements for data to be "kept for a minimum of 30 years after the expiry date of the product, unless a longer period is foreseen in the marketing authorization" is not limited to cell- based products. Indeed, it covers every form of ATMP. The guideline on GMP should be modified in accordance with the Regulation on ATMPs.

14. Quality defects and products 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.

Line 554: is it possible to give an example of such exceptional cases?

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?

Yes, although it should be highlighted that the manufacturer's responsibility for the transmission of detailed information includes the transmission of training materials for those involved in the handling or use of ATMPs, i.e. surgeons and/or other healthcare professionals.

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

Yes

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

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?

In case of use of automated devices/systems for the manufacture of ATMPs, the responsibility should be shared between the ATMP manufacturer and automated devices/systems manufacturer. The quality of the automated systems should reflect the standards specified in this document: hospitals using such systems do not have the resources to meet the quality requirements specified here. However, if specialist centres develop in the future to provide regional ATMP therapies, these should be accredited/licensed as GMP compatible.

It should be part of GMP to choose the right automated devices/systems and to use it in compliance with the techniques recognized by the automated devices/systems manufacturer and for their intended purposes. Non-compliance with these techniques and purposes should be under the responsibility of the ATMPs manufacturer/user. Problems arising from the automated devices/systems, when techniques and intended purposes required have been applied by the ATMPs manufacturer/user, should fall under the responsibility of the manufacturer of the automated devices/systems.

It is not so clear in the guideline who 'the ATMP manufacturer' is, separate from the device manufacturer. Arguably the ATMP manufacturer in the hospital is the hospital itself as a legal entity, or possibly its employees i.e. clinicians, technicians etc?

It appears necessary to clarify who the users of the automated device are regarding the ATMP manufacturer. There is an issue of how much the device users can modify its operation e.g. processing time (for instance, if surgeons modify a prosthetic device in the NHS, responsibility for its performance passes to them from the manufacturer).