

CONSULTATION ON GMP FOR ADVANCED THERAPY MEDICINAL PRODUCTS

EPSRC CENTRE FOR INNOVATIVE MANUFACTURING IN REGENERATIVE MEDICINE RESPONSES

The Centre for Innovative Manufacturing in Regenerative Medicine (the Centre) welcomes the opportunity to comment on the consultation on GMP for ATMPs and its intent to adapt GMPs to the specific characteristics of ATMPs in response to the above.

Considering the stakeholder recommendations in the European Commission's report on the EU public consultation on the ATMP regulation, it is clear that the regulatory requirements for the manufacture and QC of diverse and often individualised ATMPs under GMP is complex and not easily satisfied, especially for small companies and non-commercial organisations including key clinical centres of excellence. It is also clear that the dossier requirements, in terms of the data package, are not sufficiently adapted to ATMP development and to the available commercial models for centralised and distributed manufacture.

2.1 GMPs for ATMPs: general principles (comments on Section 2 of the consultation document)

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.

Currently, the existing EU Guidelines for GMP for Medicinal Products are ostensibly applicable to all stages of (PI to PIII) clinical manufacture (Annex 13) and already identify the need for quality risk management (QRM) programmes in line with ICH Q9 (Annex 20). The Centre supports the general principles laid down in section 2 of the consultation document and believes that the GMP requirements for ATMPs should tie in with the guidance for the Risk Based Approaches and that the level of their application should be proportionate or weighted to the ultimate risk associated with their use at each clinical development stage e.g. the number of patients in a Phase 1/First in Man study can vary and hence so does the risk. Furthermore, we believe that this should also apply to the manufacture of ATMPs under the current 'specials' provision in the UK.

We believe that it is not appropriate for small companies or non-commercial organisations that are transitioning from non-clinical to clinical manufacture to be compliant with many of the requirements in the existing GMP guideline (Volume 4) given the exploratory nature of first-in-man studies. For example, it is sometimes necessary to utilise raw materials and techniques that are better suited to research activities during Phase I in order to manage manufacturing overhead, contain costs of goods and avoid costs of comparability/validation studies with new materials/equipment that were not required under earlier phase quality practices.

Improved guidance that bridges the gap between where GMP starts and where other quality practice ends e.g. GLP and that relates to which sites are used for each element of the manufacturing and clinical process would be welcomed. The guidance provided by the USFDA for the manufacture of drugs and biologics for Phase I trials in the US for example

provides a more graded approach to GMP that is appropriate to the stage of development i.e. manufacturers are exempt from many of the requirements in CFR Part 211 during Phase I. In striving to balance patient risk (and potential benefit), a similar approach in Europe may promote innovation and early progression of promising ATMPs into clinical development resulting in accelerated clinical experience in the regenerative medicine space. There is also an opportunity to learn with respect to Quality Person (QP) backgrounds and training from some large US clinical centres, where the designated clinicians are responsible for product release.

By prioritising the chemistry, manufacturing and control (CMC) elements (Module 3 of CTD in EU) of the development process based on the criticality of the risk, a more scientific and risk based approach will facilitate such a progressive implementation approach in GMP and QS expectations, equipment qualification, analytical method validation, bioburden controls and process validation for example. However, although existing guidelines recognise the importance of QRM, the use of risk management in the Regenerative Medicine Industry has to date been limited. Its full benefit as a valuable component of the Quality System and the regulatory flexibility that it affords has yet to be realised and there is little evidence of the acceptance of such approaches by both the CAT and CHMP [M. Kooijman, 2013; Salmikangas et al, 2015].

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 different risk factors associated with the individual risks related to clinical use are mainly product specific but nevertheless multifactorial and linked to the nature/composition of the product, the starting materials and manufacturing process, as well as non-clinical and clinical aspects. Further guidance is required to better understand how risk management methodology and risk based approaches accepted under existing guidelines (e.g. ICH Q9, EMA Risk Based Approach) may be integrated and applied in practice for the various ATMP types and associated risk profiles.

To ensure consistency and understanding, it is essential to have clear and concise guidance to ensure that manufacturers submit an appropriate data package. This guidance needs to be explicit in terms of the criteria for justifying the amount and depth of quantitative data and/or published information used to address the interconnection of the quality/clinical risk factors at each stage of development (i.e. IMPD and MAA). It also needs to clarify the criteria for justifying the scope of the control strategy, the selection of critical control parameters and the distinction between those tests selected for release of goods and those carried out 'for characterisation information' which will contribute to trend analysis in the Quality Reviews and as the basis of comparability protocols and risk management plans in later manufacture.

As previously mentioned, this should be supported by guidance on how to apply a risk based approach to proportionality of the quality, non-clinical and clinical dossier content as specified in 2009/120/EC and practical examples of the application of such proportionality during development and at MAA would be highly beneficial.

2.2. Views on the GMP and Quality System requirements for combined ATMPs

Under the existing regulatory frameworks in the EU, when both the ATMP and medical device constituent parts are being manufactured at the same facility, the manufacturer is required to receive a separate authorisation for the device component in addition to review of the MAA for the cell-based component. Each statutory framework is tailored to very different product characteristics, requiring specific provisions, such as the need for design control, which create a significant regulatory compliance burden for manufacturers.

A separate guidance document for the manufacture and development of such ‘single entity’ combined ATMPs will be useful for developers of combined ATMPs. This should provide an integrated approach to development of such products and detail the standards expected i.e. a European equivalent to the final rule on GMP requirements (as defined under 21 CFR 4) for combination products implemented by the USFDA. If this can fit national GMP inspectional frameworks, this may offer manufacturers of combination products containing ATMP and device constituent parts some flexibility in terms of how operational compliance to the varying Quality System requirements can be achieved. By providing ways to streamline the overlapping aspects of development and the requirements for manufacture, unnecessary duplication and redundancy can be avoided, reducing operational and quality system costs as well as implementation times.

2.3 Views on GMP and Quality System requirements for 3D-bioprinted ATMPs

Additive manufacturing or 3D-printing is an emerging production alternative enabling manufacturers to design and build customised, anatomically-matched functional 3D tissue engineered constructs by simultaneously placing living cells into defined spatial locations within customisable scaffolds using computer-assisted design and manufacturing models derived from CT scans or MRI of the patient’s anatomy. However, despite recent progress in bringing 3D-printed medical devices to clinical use, industrial manufacturers of 3D-bioprinted tissue engineered combination products face many unique scientific and regulatory hurdles that result from the ability to create customised products, in addition to the challenges that 3D-printing will pose for conventional manufacturing paradigms.

The regulatory routes for tissue engineered combination products are complex although relatively well defined, but do not address the differences between products (or their structural parts) manufactured using 3D-printing technology and those manufactured using conventional manufacturing techniques. The use of 3D-bioprinting technology and the customisable nature of these 3D functional living constructs impose constraints on the CMC elements of their development process from design to manufacture and add considerable challenges for product quality assurance and testing.

If 3D-bioprinting is to achieve its promissory vision and expectations, new and proportionate regulatory science approaches are likely be required to address concerns that surround aspects related to how these customisable product types can be tested and validated. Linked to the current FDA activity in the US, early guidance to show the EMA’s current thinking on such developing issues is needed to bridge the regulatory gap for customised combination product manufacturers. This would give confidence to innovators who wish to ensure that their strategy for compliance will align with principles that are expected by the Competent Authority.

3. Premises (comments on Section 4 of the consultation document)

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.

As a complex, administration-intensive, costly and time consuming undertaking, qualifying cell processing facilities for GMP compliance in small-scale, resource-limited academic, hospital or small company settings can be a significant challenge, especially if they have limited pre-existing QA or manufacturing infrastructure.

As described in section 4 and 5 of this document (see below), a pragmatic risk based approach to the specific requirements on qualification and validation of premises is required. Guidance will need to take account of advances in automated closed or functionally closed processing systems for cell manipulation, which, by reducing operator variation and eliminating the external environment, will likely make validation of facility infrastructure and the manufacturing process intrinsically more straightforward and cost effective, besides being more amenable to change control and the demonstration of comparability.

4. Qualification and validation (comments on Section 10 of the consultation document)

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.

With limited manufacturing experience and under traditional process validation approaches (with the use of a limited number of product consistency lots) and end product quality control systems, manufacturing processes are often poorly specified and locked in to narrow specification criteria at the time of approval.

Where appropriate (with justification) the process validation requirement should be adjusted so as to permit and to encourage greater use of continuous verification procedures as a more progressive and graded approach. These should be conducted in line with the Real Time Release Technology philosophy by linking system response during manufacture to the quality of calibration sets of engineering product batches made during development. A combination of the two can form the basis of evolving process control strategy for increasing confidence over time as the batch history increases.

The challenge for autologous cell therapy manufacturers, in particular, is in how to apply process validation to a manufactured lot of patient cells when that same lot is intended for treatment of the patient. Whilst the recent revision to Annex 15 to bring it into line with ICH Q8-Q11 and the lifecycle approach is welcomed, greater detail on the applicability and appropriate use of concurrent validation would be of benefit. Under USFDA process validation guidance for example, the process performance qualification protocol can be designed to release process performance qualification lots for patient treatment before complete execution of the protocol steps and activities, i.e. concurrent release. Samples from each lot or a significant proportion of lots can be evaluated in a more extensive biosafety testing program in non-clinical models. This would provide statistical confidence that clinical

product manufactured by means of the qualified process routinely exhibit consistent potency while data are accrued in clinical practice under a continued process verification phase. These approaches will call for an evaluation of safety specifications that take into account the benefits of the cell therapy, corresponding levels of perceived risks, the possible practical limitations and the possibilities for risk mitigation and management. It is important to recognise that a key component of the practice of medicine is to manage the consequences of patient and disease variation. There needs to be a clearer understanding of the interfaces between the requirements of GMP and the practice of medicine.

5. Automated production of ATMPs (comments on Section 17 of the consultation document)

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?

It is imperative that the GMP obligations should keep pace with technological developments and retain flexibility to adapt to future developments. An area that is unclear within the current GMP guidelines is that of closed or functionally closed automated devices that can be used in a hospital setting to process cells intended for human use.

These devices have tested the regulatory paradigm by being approved as medical devices to process autologous cells for re-injection during the same surgical procedure. These devices select cells and as such the cells may not be considered substantially manipulated, as defined in Annex 1 of 2007/1394. However, if the cells are used for a non-homologous application, or if the cells are more than minimally manipulated the question arises as to whether the system should be validated as a piece of equipment or as a device for producing a product licensed under ATMP regulations, requiring a Manufacturers Authorisation with QP certification for the device in each hospital setting.

These closed or functionally closed manufacturing devices offer an attractive solution to the logistical issues posed by traditional manufacturing supply of short shelf-life cells and due to technical progress, their anticipated use is increasing. A requirement for a Manufacturer's Authorisation for each hospital facility however will be extremely challenging.

The Centre believes this area needs to be explored and guidance produced. We believe that engineering and production system design solutions to the development of highly standardized, closed or functionally closed automated production systems could provide opportunities to exploit the potential for locating closed processes and their supporting systems within non-classified room environments, or so-called Controlled Not Classified manufacturing settings. This could potentially lower infrastructure and operational costs and the time and cost involved in regulatory compliance for both existing and new facilities.

We believe that a closed or functionally closed automated production system, by removing operator variation and the external environment, that is, the extrinsic contamination risk from the manufacturing process, will bring the process under control and make process variation

more predictable. Process development and validation would be intrinsically more straightforward, provided it was founded on Factory Acceptance Testing of the built system and its qualification at each site (including the software). The machine and the location or space in which it is housed would need to be controlled and maintained under a Quality Management System for every manufacturing and QC step, whether it is installed in the factory, in the hospital or at the bedside. This would necessarily involve evolving GMPs that are better suited to the setting in which the closed or functionally closed manufacturing takes place, for example, GMPs for nurses or health professionals. Under these practices, appropriate risk-based approaches for controlling the risk of contamination and ensuring safe operations can be used to define the level of process and facility hygiene control and to mitigate risks of human error or interference with system hardware and controlling software.

Based on the above, our assertion is that these so-called “GMP in-a-box” devices could be validated to design specifications by means of a cell/product-specific protocol within a fully closed processing environment. A single Manufacturing Authorisation would be required, but only the machine would need to be validated for a chosen indication/protocol and not the sites in which it would be used. Optionally there may be a requirement for the support services (QP oversight, management of training and maintenance) for the devices to be considered as a licensable operation as it is on this basis that the assurance of quality is made rather than the geographical location.

We believe flexibility in approach for this type of Manufacturing Authorisation will be required as will detailed guidance on GMPs that are better suited to the setting in which the closed or functionally closed manufacturing takes place. This guidance would need to clarify for example, where GMP starts for a bedside device producing an ATMP, how these closed or functionally closed systems must fit the environment in which they are housed and how both can be inspected, how lot release criteria for potency and the fidelity of the products they produce is determined and the practicality of procedures by which an appropriately qualified person can release the final product that is produced for immediate administration into the patient.

6. Conclusion

The Centre welcomes the opportunity to take part in the GMP for ATMP guidance review. In moving away from pre-defined programmes for ATMP development, it is clear that a flexible, risk based approach with proportional data requirements is desirable for manufacturers and will be beneficial to progression of the industry as a whole.

It is hoped that this review will lead to an improved interface between GMP and the other quality practices applied across the product development lifecycle and may lead to more detailed integrated guidance on how to apply risk based approaches across the ATMP development process. Further discussion and guidance for the various product family types throughout the various stages of development in the areas highlighted in this document would be welcomed. For example, early guidance to show the EMA’s current thinking on emerging issues for combination products (conventional and 3D bioprinted), which provide a regulatory bridge between ATMPs and medical devices, will be of significant value to manufacturers.

If the regulatory framework continues to adapt to rapid scientific progress and technological advances in cell-based therapy manufacturing, as an industry we believe that manufacturers

will be able to derive and implement better and more effective ways of qualifying their facilities, equipment and automated manufacturing systems. This will ensure that facilities and manufacturing systems are delivered fit for purpose and capable of supporting the reproducible manufacture of quality cell-based autologous therapy products across multiple manufacturing sites while controlling risk to patient safety.