

EC REVIEW OF THE ATMP REGULATION – CELL THERAPY CATAPULT RESPONSES

1 Introduction

It is clear from the very small number of MAA approved to date that the registration process for ATMPs is complex and not easily satisfied. There are many and diverse ATMPs progressing through development aimed to address significant unmet patient needs and the Cell Therapy Catapult welcomes the opportunity to comment on the ATMP regulation 2007/1394.

The regulation was required because of the expansion of new cellular derived therapeutics and successfully effected the inclusion of these products in medicinal legislation (2001/83/EC). Further documents such as the stem cell reflection paper¹ and revision to Eudralex volume 4 (particularly Annex 2) have further helped to advise the developers of such products. However the field is rapidly developing and further guidance is required.

In addition, it is clear that there is still confusion of the interaction between Regulation 2007/1394 and the Tissues and Cells (2004/23/EC) and Blood (2002/98/EC) Directives and the translation of these Directives into member state law. This becomes apparent in disharmony of enforcement in member states and in the information looked for by competent authorities during inspection and assessment. Further common sources of uncertainty are detailed individually below.

2 Questions posed in the consultation document

2.1 Requirements for marketing authorisation applications set out in the Regulation

2.1.1 Dossier Content

It is clear that the classical CTD structure of an MAA dossier is not suitable for the majority of ATMP products. For example, the concept of a drug substance may be suitable for some large scale products, but clearly does not apply to small scale autologous and allogeneic open culture derived products e.g. ex vivo expanded stem cell products from adult cells. Similarly, the validation of processes cannot easily follow revised expectations arising from Quality by Design concepts, and both classical preclinical testing and traditional large double blind, randomised, controlled clinical trials are simply not possible for many ATMPs.

Consequently, flexibility in the data package to be presented as part of an MAA, as suggested in the MHRA's Early Access Adaptive/Conditional Licensing options, is necessary. The proportionality of the requirements to the clinical need/size of the patient population is suggested by the draft publication of the risk-based approach (RBA²) along with improved guidance on the requirements for the various product types will facilitate this.

To ensure consistency and comprehension, it is essential that groups developing such products have clear and concise guidance to ensure that they submit a suitable data package at each stage of development (i.e. IMPD and MAA) and assessors of those products have the freedom to be flexible in their assessment. Further guidance on how to apply a risk based approach to proportionality of a dossier and practical examples of the

¹ EMA/CAT/571134/2009 [Reflection paper on stem cell-based medicinal products](#)

² EMA/CAT/CPWP/686637/2011 Draft guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products

application of such proportionality during development and at MAA would be welcomed. It would also be very reassuring for stakeholders, such as investors, to be able to see the acceptance of such approaches by both the CAT and CHMP.

2.2 Views on the foreseen authorisation procedure for combined advanced therapy medicinal products

The legislation suggests that the device component of a combined ATMP must receive a separate licence (CE mark) in addition to review of the MAA for the cell-based component. This is logical for those devices that will be sold separately, but if the device component forms an integral part of the ATMP and is not manufactured as a separate entity, this may lead to a significant regulatory burden, especially if the device component is considered to be in Class IIB or Class III. A separate guidance document for the manufacture and development of combined ATMPs may therefore be useful for developers of combined ATMPs, detailing the standards expected i.e. a European equivalent to the final rule on the regulation of combination products promulgated by the USFDA.

We suggest that the subsequent 'approval' of the device could be performed by suitably trained Device assessors who will take part in the MAA assessment, dependent on the role of the device and the level of interaction and manipulation of the device with the cellular material. This allows for a single assessment process and removes any disparity that could arise between different Notified Bodies (NB) or between a NB and the CAT / CHMP. Under both of these circumstances there would be no need for a separate CE mark to be given to the device component used only in the manufacture of a specific product.

2.3 Application of the hospital exemption clause

The hospital exemption (HE) clause is an important piece of legislation that allows ATMPs to be used for non-routine procedures under the exclusive responsibility of a medical practitioner solely for use within that member state. Therefore HE can play an important role in allowing patients to gain access to potentially life-saving unlicensed products and assist in the innovation process for those investigating the potential clinical utility of new treatments. However there is uncertainty on what constitutes routine use and there is disparity of the requirements between member states.

The following are considerations that the Cell Therapy Catapult believed will permit both the correct use of the HE clause without compromising the integrity of the clinical development process for ATMPs:

- HE licences should not be granted to treat patients for an indication where there is a licenced ATMP available. It is proposed that the only exception to this rule is in instances where a specific sub-population of patients exists that cannot be treated adequately with the licensed product, or where there is a shortage or a failure to supply the licensed product.
- The definition of routine and non-routine use appears to be left open to interpretation across different member states. EU intervention to provide clarity on this would be welcomed. The concern is that without a clear definition, HE therapies will be used on a more routine basis than was intended, reducing the incentive to take ATMPs through the clinical development and licencing process.

2.4 Approval process

The Regulation requires that all MAA are assessed through the centralised procedure. This was a requirement to ensure that there was an appropriate pool of expertise to advise and assess these new and emerging products. The Cell Therapy Catapult believes this is commendable however the centralised procedure is a considerable regulatory hurdle for small companies and non-commercial organisations. The Cell Therapy Catapult believe that a tiered approach to licensing as discussed above with an option for adaptive/conditional licensing for life-saving products for patients with immediate need which allows early access to these medicines but with the requirement for continued data-gathering during use both pre and post licensing.

2.5 Incentives provided for under the Advanced Therapy Regulation

2.5.1 Revision of the Certification Procedure for Non-Clinical Data

The outcome of the CAT survey on the certification procedure³ demonstrated that generally the SMEs who responded thought that the certification procedure was of value and would consider applying. In particular they thought certification would help in commercialisation and in / out-licensing. However the scope of the certification procedure and overlap with other EMA related procedures needs to be strengthened /clarified and the limited uptake is also of concern. The Cell Therapy Catapult supports the suggestion to extend the scope of the certification procedure, which is currently restricted only to SMEs developing ATMPs, to include research groups and academia. It may also be that the certification system should be better promoted to provide greater assurances over the validity of the service. In addition the certification of a Stem Cell History File should be considered.

2.5.2 Revision of the GMP Requirements for the Manufacture of ATMPs during Phase I Clinical Trials

Currently, the guidelines provided in Annex 13 are ostensibly applicable to all stages of clinical manufacture (PI to PIII). The Cell Therapy Catapult believes that the GMP requirements for ATMPs should tie in with the draft guidance for the RBA discussed in 2.1 and the level of their application should be appropriate to the ultimate risk associated with their use e.g. the number of patients in a Phase 1 / FiM study can vary and hence so does the risk.

Furthermore, it does not seem appropriate for those manufacturers that are moving from non-clinical to clinical manufacture, to be compliant with vast majority of requirements in Volume 4 given the exploratory nature of first-in-man studies. For example, it is sometimes necessary to utilise raw materials (see 2.7.1) and techniques (e.g. FACS) that are better suited to research activities during Phase I in order to avoid burdensome comparability / validation studies with new materials / equipment that were not required for GLP. Guidance that better bridges the gap between GLP and GMP would be more suitable. The guidance provided by the USFDA for the manufacture of drugs and biologics for Phase I trials has been welcomed by manufacturers in the US as it 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. A similar approach in Europe may

³ Outcome of the EMA survey on ATMP certification for SMEs - Commission Regulations (EC) No. 1349/2007 and No. 668/2009

incentivise developers of ATMPs and expedite the number of ATMPs moving into clinical development before progressing to the guidelines provided in Annex 13.

2.5.3 Fee Reductions for non-commercial Institutions

A recent study by the Cell Therapy Catapult⁴ indicated that of the 21 clinical trials currently taking place in the UK involving ATMPs, only six are led by commercial sponsors, with the remainder led by academic and research institutions. This indicates that the largest concentration of development work in the UK is being done outside of commercial companies. This conclusion was also reached in a recent publication on ATMPs in the EU⁵.

The fees payable to the EMA for scientific advice are currently not reduced for academic institutions. The EMA definition of a SME requires the company to prove that they are an autonomous organization that is not governed / controlled by a publically funded body which is not possible for academic and publically funded hospitals. Academic groups have indicated that the size of the fees is discouraging them from developing their technologies further as they cannot justify the fees within their tight budgets and spending restrictions. The acute danger is that without access to scientific advice at key points during the development process, these non-commercial led technologies will not be able to efficiently progress and this is the feed-stock of innovation for this industry and to meet patient need. The Cell Therapy Catapult strongly supports a similar fee reduction for public health bodies and Universities to that available for SMEs.

2.6 Scope of the regulation and in particular as to whether the scope should be modified to take account of technical progress.

It is imperative that the ATMP Regulation keeps abreast of technological developments and retains flexibility to adapt to future developments. Early guidance to show the EMA's current thinking on such developing issues e.g. autologous iPS cells which provide a regulatory bridge between CBMPs and gene therapies, will be of significant value to researchers.

One example of an area that is unclear within the current Regulation is that of closed system devices that are used 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 Annex1 of 2007/1394. However, if the cells are used for a non-homologous application, the question arises as to how they will be regulated and a Manufacturers Licence with QP certification is needed for the device in each acute hospital setting. These 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 Licence for each hospital will be extremely challenging. The Cell Therapy Catapult believes this area needs to be explored and guidance produced. We believe flexibility in approach for this type of Manufacturing Authorisation as described above for Marketing Authorisations will be required This will ensure that innovation is not stifled and the regulations surrounding European trials are not prohibitive.

⁴ Cell Therapy Catapult website publication on UK cell therapy clinical trials <http://catapult.org.uk/celltherapy>

⁵ Maciulaitis *et al*, Molecular Therapy Volume 20, No 3, March 2012, pp 479-382

2.7 General comments

The Cell Therapy Catapult appreciates the possibility to comment on these specific topics, however there are many other topics which could be similarly discussed and some of these are detailed below.

2.7.1 Quality of raw materials

Although this topic is currently the focus of a study by the EMA / EDQM, there is still much confusion over the terminology used to describe their quality. For example, the use of “GMP”, ATMP ready and “clinical” grade are commonplace, but the interpretation of these terms can vary according to both the supplier and the end user. One possibility that could ease the burden of risk assessment could be a scheme similar to the EDQM Certificate of Suitability which could be used for the certification of widely used reagents. Furthermore the requirement to use GMP reagents during product development could be clarified as our comments on ‘graded GMP’ during development in section 2.5.2 above.

In addition there is disparity in the traceability requirements between the Article 8 of EUTCD (2004/23/EC) and Article 15 of Regulation 1394/2007, harmonisation of such requirements will aid companies in the development and compliance with such products.

2.7.2 Non-clinical development

The use of animal models in the non-clinical evaluation for cellular therapy products is addressed in part by the Stem Cell Reflection paper¹. This paper acknowledges that appropriate animal models may not be available and discusses the uncertainty of the similarity between animal and human stem cells or factors that may limit the predictive ability of such a model. However, it states that non-clinical evidence on the proof-of-principle and safety of the stem-cell based product in a relevant animal model is expected before administration to humans. It would be helpful to understand further the current thinking on areas such as requirements for non-clinical data when clinical data are already available and acceptable alternatives when there are no suitable animal models.

2.6.3 Characterisation

The characterisation of cellular therapy products is complex, mixed populations are common and there is intrinsic biological variability which is often compounded by the small volume/amount of finished product. Whilst specific guidance is simply not feasible for many product types, more detailed guidance is welcomed on the requirements of the various ATMP product families, particularly autologous therapies, small scale expanded explants and tissue engineered therapies.

2.6.4 Stability testing

The small amounts of product and short shelf-life will make ICH compliant stability testing impracticable. Guidance on acceptable data sets would be welcomed.

3 Conclusions

The Cell Therapy Catapult welcomes the opportunity to take part in the ATMP regulation review. It is clear that a flexible, risk based approach with proportional data requirements is desirable for manufacturers, regulators and patients.

It is hoped that this review will lead to improved interface between the Regulation and the Blood (2002/98/EC) and Tissues and Cells Directive (2004/23/EC) and may lead to more detailed guidance on the development and testing (non-clinical and non-clinical) of cellular ATMP. In addition it is hoped that the incentives available for SME are expanded to cover non-commercial organisations. 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.