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Your Ref
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Dear Sirs

PUBLIC CONSULTATION ON THE REGULATION OF ADVANCED THERAPY MEDICINAL PRODUCTS

NHS National Services Scotland (NSS) welcomes the opportunity to comment on the above consultation and does this through the context of the work of the Scottish National Blood Transfusion Service (SNBTS).

1. General

It is clear from the very small number of Marketing Authorisation Applications approved to date that the registration process for Advanced Therapy Medicinal Products is complex and not easily satisfied. Therefore this review of the Regulations with a view to simplification and clarification is welcomed. 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 paper[1] 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 (EUTCD; 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 of clinical trial documentation.

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

2. Questions posed in the consultation document

2.1. Requirements for marketing authorisation applications set out in the Regulation.

2.1.1 Dossier Content and Approval Process

It is clear that the classical Common Technical Document structure of a Marketing Authorisation Application dossier is not suitable for a large majority of Advanced Therapy Medicinal 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 for example ex vivo expanded stem cell products from adult cells. In addition the preclinical and clinical packages required for such products are quite different from that of traditional pharmaceuticals. While there is some guidance on these topics National Services Scotland feel the field would benefit from more guidance on product family requirements and a flexibility in the licensing requirements. As such National Services Scotland welcome the MHRA suggestions for Early Access, Adaptive/Conditional Licensing options in line with 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 (Risk Based Approach[2]) for this product type.

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

The legislation suggests that the device component of a combined Advanced Therapy Medicinal Products must receive a separate licence (CE mark) in addition to review of the Marketing Authorisation Application 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 Advanced Therapy Medicinal Products and is not manufactured as a separate entity, this may lead to a significant regulatory burden. National Services Scotland suggest that devices integral to combined products are assessed by suitably trained Device assessors who will take part in the Marketing Authorisation Application assessment and should not require the assessment by a Notified Body, as required in the Regulation. If the assessment by a Notified Body is to remain, then clear guidance is required for Assessors, Notified Bodies and applicants on the respective responsibilities and timelines for these separate assessments.

2.3 Application of the hospital exemption clause

The hospital exemption clause is in important piece of legislation that allows Advanced Therapy Medicinal Products to be used for non-routine procedures under the exclusive responsibility of a medical practitioner solely for use within that member state. Therefore hospital exception 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. The UK also benefits from the “Specials” legislative requirements[3] which allows products to be supplied to meet special clinical needs of a patient that cannot be met by licensed products upon receipt of a bona fide unsolicited request from a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber who are directly responsible for the use of the product. This legislation allows the distribution of the product throughout the UK and the EC. The Scottish National Blood Transfusion Service, have used this facility to supply product (anti-Epstein Barr Virus CTL product) to other member states and believe that the ability to distribute the potentially life-saving products to other EU member states should be considered in the revision of these Regulations. Furthermore the Specials legislation in the UK only permits the use of an unlicensed product if there is no licensed alternative. This is not a requirement of the hospital exemption scheme. National Services Scotland believes this may lead to disparity in

[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

[3] Article 5.1 of Directive 2001/83/EC & Article 83 of Regulation (EC) No 726/2004, enacted in the UK in Regulation 167 of the Medicines Regulations 2012 No 1916

the safety and quality of products available in various member states and would encourage this clause to be added to the hospital exception supply.

2.4. Incentives provided for under the Advanced Therapy Regulation

2.4.1 Fee Reductions for Non-commercial Institutions

Throughout the EU the vast majority of Advanced Therapy Medicinal Products are being produced by non-commercial organisations (Blood Transfusion Services, Hospitals and Academic institutions). In the UK this is estimated to be as much as 90% of Advanced Therapy Medicinal Products and related Cellular Therapies under development or in clinical trial. Such institutions are exempted from the considerable incentive initiatives offered to Small and Medium Sized Enterprises, for example 100% reduction in many fees associated with the scientific advice and registration of an Orphan Medicine. The Scottish National Blood Transfusion Service urge that the Small and Medium Sized Enterprises incentives are expanded to be available to such non-commercial organisations.

2.4.2 Revision of the Certification Procedure for Non-Clinical Data

The outcome of the Committee and Advanced Therapies survey on the certification procedure[4] demonstrated those 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 European Medicines Agency related procedures needs to be clarified and the limited uptake is also of concern.

The benefit of a development of Stem Cell History File, with a facility for certification where appropriate, suggested by the MHRA may also be another route that would allow manufacturers to be assured of the safety and quality of the starting and intermediate products while at the same time helping to ensure compliance with the Traceability requirements of all relevant legislation.

2.5 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 Advanced Therapy Medicinal Products Regulation keeps abreast of technological developments, for example iPS cells which provide a regulatory bridge between Cell Based Medicinal Products and gene therapies or the ability for autologous transplant of cells within the same surgical procedure from a cells harvested from the patient's bone marrow/adipose tissue which could be considered to fall under the remit of the EUTCD 2004/23/EC. Early guidance to show the European Medicines Agency current thinking on such developing issues will be of significant value to researchers.

2.6 General comments

National Services Scotland appreciate the possibility to comment on these specific topics however there are many other topics which could be similarly discussed, for example the potential difficulties that may arise for the requirements with full traceability on the quality of raw materials, etc. some of which are detailed below.

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

2.6.1 Quality of raw materials

Although this topic is currently the focus of a study by the European Medicines Agency/ European Directorate for the Quality of Medicines, there is still much confusion over the terminology used to describe their quality. For example, the use of “Good Manufacturing Practice”, Advanced Therapy Medicinal Products ready and “clinical” grade are commonplace but the interpretation of these terms can vary to 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 European Directorate for the Quality of Medicines Certificate of Suitability which could be used for the certification of widely use reagents. Furthermore the requirement to use Good Manufacturing Practice reagents during product development needs clarified. 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, relevant text below. The Scottish National Blood Transfusion Service suggest that potential harmonisation of such requirements will aid companies in the development and compliance with such products.

2.6.2 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 paper[2]. 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. As a consequence, there is still uncertainty in the field about what is required. It might be helpful if the Committee for Advanced Therapies where to commit to providing a database of suitable animal models for particular investigations. This database could be kept updated as developments in animal models progress. Where possible, the intended cell-based product consisting of human cells should be used.

2.6.3 Characterisation

The characterisation of Cellular Therapy products is complex and uncertain and this is compounded by the 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 Advanced Therapy Medicinal product families e.g. small scale expanded explants, autologous MSCs for infusion, large scale products manufactured from hESCs, etc.

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. Conclusion

The Scottish National Blood Transfusion Service, as a manufacturer of Cellular Therapy products welcome the opportunity to take part in the Advanced Therapy Medicinal Products regulation review. It is clear that a flexible risk based approach is desirable for both manufacturers and regulators however, for this to work practicably there needs to be clear guidance available for the various product family types throughout the various stages of development. 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 Advanced Therapy Medicinal Products. In addition National Services Scotland urge that the incentives available for SME are expanded to cover non-commercial organisations.

If you would like clarification on any of the comments made, please contact Dr Jacqueline Barry, SNBTS Regulatory Compliance Manager, on 0131 536 5763.

Yours faithfully

IAN CRICHTON
Chief Executive