EC REVIEW OF THE ATMP REGULATION
RESPONSE FROM ROSLIN CELLS LIMITED

1. Introduction

Roslin Cells Limited is an SME based in Edinburgh and operates the Cellular Therapy Facility within the Scottish Centre for Regenerative Medicine. Roslin Cells manufactures clinical grade pluripotent stem cells and intents to manufacture cellular therapy products within this custom built facility. An application has been made to the UK MHRA for licences to manufacture products for clinical trial (MIA IMP) and to manufacture products as "Specials" under the terms of the UK Medicines Regulations, 2012 (Manufacturers Specials Licence). It is expected that Roslin Cells will manufacture licensed ATMPs in due course. As a fairly new organisation which is developing expertise in the field of ATMPs, we would welcome all initiatives designed to make the regulation of ATMPs simpler and more affordable. It is clear that the available regulation is currently a bit fragmented and can be contradictory, with sometimes conflicting advice from other sources of advice such as Annex 2 to the EC Guide to GMP, and with specific Directives on Tissues and Cells (EUTCD; 2004/23/EC) and Blood (2002/98/EC) Directives and the translation of these Directives into member state law.

It is also clear that the ATMP regulation is principally concerned with the licensing process (ie the requirements for the approval of an MAA), and that the requirements for intermediate stages (master cell banks and working cell banks) or for clinical trials are not dealt with in such detail. It would be very helpful if the revised Regulation could address these intermediary stages.

It is also clear that the requirements to achieve an MAA are formidable and expensive, and not really matched to the abilities of many of the small scale manufacturers who are currently producing low volume products for evaluation. If the licensing route cannot be adapted to cope with such small scale, low volume products, there is a danger that smaller organisations and academic bodies will not progress beyond the Hospital Exemptions or Specials type of manufacture, and that they will be regulated within different countries to different standards.

2. Questions Posed in the Consultation Document

2.1 Marketing authorisation requirements for advanced therapy medicinal products.

The statement in paragraph 2 of the consultation document is critical and states in effect that there must be enough data to ensure a high level of public health protection. However, it is clear from the process so far that it has been very difficult for organisations to achieve an approved MAA. There seems likely to be a significant danger that many smaller organisations will not aspire to licensure but

to manufacture and release cellular therapy products exclusively through alternative means such as Hospital Exemptions and Specials.

Some of the complexity in this field is that the layout of an MAA dossier is still designed principally around the requirements of more conventional pharmaceutical products. Any simplification of this process encompassing the specific requirements of different types of ATMPs would be of real benefit. Specific guidance on non-clinical safety issues would be of value, since it is difficult to envisage suitable animal study protocols for some cellular therapies.

2.2 Requirements for combined advanced therapy medicinal products

Everything should be done to ensure that licensing of devices does not become an expensive addition to the already significant licensing requirements. For devices which are unique to the delivery of the ATMP, then it would be highly desirable that the assessment is conducted as part of the MAA assessment process.

2.3 Hospital exemption

The concern over the extensive use of the Hospital exemption mechanism is understandable, since as stated above, this option can be implemented more quickly and with less effort than a marketing authorisation application. This situation is further complicated by the availability of Specials legislation in the UK and some other EC countries. It is not straightforward to see how this can easily be dealt with. In the short term, it would be very helpful if guidance could be given on the minimum GMP and regulatory requirements which should be adopted by manufacturers who plan to use either of these routes for product release. This would have the extra benefit of harmonising standards in different member states.

2.4. Incentives for the development of advanced therapy medicinal products

Any incentives which assist in the development of this type of cutting edge therapy should be considered worthwhile. The existing incentives are considered highly valuable, but it would be worth extending the incentives to not for profit organisations other than hospitals. In the UK, this would include Blood Transfusion Services and University Departments, both of which have a significant role in the development and manufacture of ATMPs.

Many of the raw materials currently used in the manufacture of ATMPs are common to many manufacturers, and some of these can only be obtained currently as non-GMP grade. A significant

incentive to organisations contemplating moving into this field would be the development of a certification scheme for this type of material.

2.5 Scope and adaptation to technical progress.

There is already some confusion between the overlap between ATMPs, blood and tissues. Any further clarification on this topic would be most welcome, particularly since the classification of such products can have a massive impact on the extent and type of documentation required. As stated earlier, different types of ATMP require different approaches to documentation and development. This topic is addressed in Annex 2 to the EC Guide, but any further consideration would be welcome.

There are already a number of individual guidance documents on aspects of GMP relating to ATMPs (eg on CJD risk). It would be very helpful if this guidance could be brought together when the Regulation is revised.

It is imperative that the ATMP Regulation keeps abreast of technological developments in this rapidly evolving field.

2.6 General comments

There are a number of other issues which are not specifically included in the consultation which would be worth considering in the review of the Regulation

2.6.1 Quality of Raw Materials

As stated earlier this is a large and complex issues and more guidance on this topic would be welcome, particularly relating to the use of reagents declared by the manufacturers to be for research use only and for which there are no satisfactory alternatives.

2.6.2 Products With Short Shelf Lives

Many ATMPs are issued with exceedingly short shelf lives and cannot be fully characterised or tested prior to release. Any guidance on this topic would be very welcome.

2.6.3 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

Roslin Cells are delighted to be able to participate in this consultation and look forward to reviewing the revised Regulation in due course. The particular issue of concern is to ensure a regulatory mechanism which is sufficiently flexible and transparent that appropriate, successful MAAs can be achieved by an SME such as Roslin Cells.