European Commission public consultation on the Regulation on Advanced Therapy Medicinal Products

UK BioIndustry Association Response

About the UK BioIndustry Association (BIA)

Established in 1989, the BioIndustry Association (BIA) is the trade association for innovative healthcare focused bioscience enterprises. BIA members include emerging and more established bioscience companies, pharmaceutical companies, academic research and philanthropic organisations, and service providers to the UK bioscience sector. Our members are responsible for over ninety per cent of biotechnology-derived medicines currently in clinical development in the UK and are at the forefront of innovative scientific developments targeting areas of unmet medical need. This innovation will lead to better outcomes for patients, to the development of the knowledge-based economy, and economic growth.

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General comments

1. The BIA welcomes the opportunity to respond to the European Commission's public consultation on Regulation 1394/2007 on Advanced Therapy Medicinal Products (hereafter referred to as the ATMP Regulation). We believe this consultation is timely and will be a useful exercise in considering the practical implementation of the ATMP Regulation and its effect on the research and development of such products.

2. In preparing this response the BIA has engaged with experts from its membership representing both large global biopharmaceutical and small emerging bioscience companies operating within this field. Before answering specific questions below the BIA can make some overarching comments regarding the ATMP Regulation to place our answers in context and provide some background.

3. UK strength in ATMPs: The UK remains a world leader in developmental biology, cell and stem cell research. It possesses a large academic capacity with multiple academic centres of stem cell research excellence grounded with continued commitment from public funders of more than £100 million for basic research. There are also significant levels of financial support and engagement from medical research charities including the Wellcome Trust, British Heart Foundation and UK Stem Cell Foundation for example.

4. Successive UK governments have also demonstrated support for the emerging field of ATMPs. This can be highlighted by the newly established UK Cell Therapy Catapult which will provide a centre of excellence for the development, delivery and commercialisation of cell therapies. The UK Technology Strategy Board (TSB), an agency to support the development of innovation, has also supported a number of companies with regenerative medicine specific funding opportunities.

5. The increase in research and development of ATMPs in the UK can be highlighted by the increase in trials involving such products[1]. Moreover, the Medicines and Healthcare products Regulatory Agency (MHRA) now provides around twenty five scientific advice meetings specifically in the field of ATMPs per year.

6. ATMPs globally: Regenerative medicine cell-based therapies are already in routine clinical practice. For example, today there are seven US Food and Drug Administration (FDA) approved cell-based therapies. In the period between 1998 and 2010 over a third of a million patients have been treated with these products, resulting in improved patient outcomes and quality of life for patients. The overwhelming majority of treatments have taken place in the US and there is a need to improve their uptake in the EU.

7. Legislative framework: Any review of the ATMP Regulation must not look at this piece of legislation in isolation as there are many other aspects of European law which impact upon the research and development of such products. These include: a) the Clinical Trials Directive and the proposals for a new Clinical Trials Regulation currently undergoing legislative scrutiny; b) the Genetically Modified Organisms Directive; c) the new Pharmacovigilance Regulation and in particular new approaches to risk-adapted pharmacovigilance activities; and d) the legislative framework underpinning the development of Orphan drugs in the European Union including Regulation (EC) No 141/2000. This is particularly relevant as a number of ATMPs under development will be for the treatment of rare diseases and as such be eligible for EU Orphan Drug status which brings with it a number of incentives including expedited regulatory approval and increased data exclusivity periods.

8. Interaction of regulatory bodies: Following the above, it is also important to bear in mind the need for frequent and open dialogue between the various regulatory bodies responsible for the development of ATMPs. For example, a company developing such products in the UK will be mindful of interaction with the MHRA, the Human Tissue Authority (HTA) and the Human fertilisation and Embryology Authority (HFEA) at a national level as well as the European Medicines Agency (EMA) and Committee for Advanced Therapies (CAT). There is therefore a need for a consistent and joined-up approach to ATMPs from regulators.

9. Stage of development of ATMPs: This consultation primarily focuses upon the incentivisation of late stage development work and marketing authorisation (MA) applications. While this is clearly important the BIA would also urge the European Commission to give due regard to the incentivisation of earlier research and development and the support that is necessary at those stages. This is of importance given the increasingly collaborative nature of such research and development involving partnerships between academia, public funders, small and emerging bioscience companies and global biopharmaceutical companies. The regulatory framework for early stage research must be conducive to such collaborations.

[1] Mason C. & Manzotti E. Regenerative medicine cell therapies: numbers of units manufactured and patients treated between 1998 and 2010. Regen. Med. 2010, 5(3), 307-313.

Response to specific questions

10. The BIA would like to focus its comments on two specific questions outlined in the public consultation document.

2.1 Marketing authorisation application requirements for advanced therapy medicinal products

11. As stated in the public consultation paper, the ATMP Regulation provides for adapted requirements in terms of the dossier that applicants are required to prepare to demonstrate quality, efficacy and safety when applying for MA.

12. In general, it is the BIA's view that the ATMP Regulation has had a positive effect in encouraging innovation in the emerging area of ATMPs. The European Union has developed a robust regulatory framework for such products that many other jurisdictions could usefully learn from. There is now an opportunity to further enhance and refine the practical implementation of the ATMP Regulation to ensure it remains effective, relevant and progressive.

13. While this may generally be the case, it is considered that there are a number of areas which are hindering progress which could usefully be addressed by the Commission and which are outlined below.

14. The MA requirements for ATMPs currently represent a high barrier for innovative companies developing such products. This assertion can be supported by the fact that in the five years since the implementation of the ATMP Regulation only two products have been approved.

15. The uptake of one of those products (ChondroCelect), the first approved ATMP in Europe, is being undermined by the application of the hospital exemption in Europe (see below for further details). The other product (Glybera), the only approved gene therapy product in Europe was subject to a complicated, burdensome and expensive appeals process involving the CAT, Committee for Medicinal Products for Human use (CHMP) and the European Commission.

16. This has left an uncertain environment for companies developing such products to operate in and is contrary to the aims of the ATMP Regulation to stimulate further development in this field in Europe for patient benefit. This cannot be considered a satisfactory state of play.

17. The BIA recommends that it should be acknowledged that ATMPs do not present a uniform risk across different classes of products (e.g. patient specific autologous somatic cell therapies may be considered to be lower risk than tissue engineered products). There may be opportunities for the EMA to facilitate the authorisation of 'lower risk' products through a risk-adapted approach. This may offer opportunities for conditional approval of products with significant clinical benefit upon the condition of gathering additional safety and efficacy data. Parallels to this approach may be seen with pandemic influenza vaccine MA procedures for example. This might serve to instil greater confidence amongst companies.

18. It is recognised that there is a need for additional ATMP MA requirements regarding post-authorisation follow-up of efficacy and adverse reactions, risk management and traceability. Some of these requirements can be considered proportionate measures in light of the potential risks associated with ATMPs.

19. However, there is concern that the 'standard' MA requirements are being applied more stringently to ATMPs than to existing small molecules and biological medicinal products unfairly and beyond what is proportionate.

20. Further, while the BIA supports the requirement in Article 15(2) for traceability linking of each product to the patient who received it and vice versa, Article 15(1) is considered an unnecessary and unjustified burden on MA holders to maintain a traceability system for all substances coming into contact with cells and tissues. If interpreted broadly and to its natural conclusion, the requirement to consider all substances would needlessly result in the inclusion of pipettes, incubation flasks and the water used for incubation solutions for example. The intention behind this was most probably the requirement to ensure traceability of substances that may affect product quality or safety (such as materials of biological origin) and therefore clarification and additional guidance are sought.

21. Moreover, responsibility for the fulfilment of requirements in Article 15(2) are not sufficiently clear in the Regulation. It is the BIA's view that this aspect of traceability, i.e. traceability from the institution to the patient, should be the responsibility of the institution and may require the development of further practice guidelines to provide greater clarity to the sector. As a general point, the applicability of such traceability provisions for specific ATMPs should be considered on a case by case basis.

2.3. Hospital exemption

22. As stated in the public consultation paper the ATMP Regulation empowers Member States to authorise the use of ATMPs in hospitals for individual patients in the absence of a marketing authorisation. This was also to be performed on a non-routine basis.

23. The BIA supports the hospital exemption as an important opportunity for patients to receive treatment in the absence of a marketing authorisation and where no alternative exists. However, as alluded to in the public consultation paper, the significant application of such a provision, e.g. on a routine rather than non-routine basis, may disadvantage companies, disincentivise MA applications and ultimately disincentivise investment into research and development of ATMPs.

24. Unfortunately this eventuality is now a practical reality in the field of ATMPs. The application of the hospital exemption is demonstrably leading to an unlevel playing field. Companies must adhere to strict regulatory requirements within a robust regulatory framework as they develop their product whereas the production and use of such products in hospitals is now moving beyond the non-routine basis envisaged within the ATMP Regulation.

25. This situation acts as a disincentive for the research and development of ATMPs in Europe and is also not optimal with regards to guaranteeing a high level of health protection for European patients treated with ATMPs.

26. Furthermore, the situation is mixed throughout EU Member States without consistent application. This can clearly be demonstrated by reference to the paper '*Hospital exemption for ATMPs (implementation of Art 28(2) of Regulation 1394/2007): update on feedback received by the Commission*' which was discussed at the European Commission's Pharmaceutical Committee on 22 October 2012. A summary of the application of the hospital exemption in different Member States shows a wide divergence of practice. In some cases no guidelines exist at Member State level.

27. It is the BIA's considered view that this mechanism should only be used in exceptional circumstances. Individual health authorities should apply the hospital exemption with substantial rigour, ensuring treatments provided under the hospital exemption meet equivalent standards as those expected for a marketing authorisation. Consistent application between Member States is also vital.

28. It is suggested that one possible solution is following authorisation of an ATMP an element of protection is achieved by preventing the application of the hospital exemption for similar products with the same indication. Similar to patient supply or compassionate use the BIA would expect that once a fully authorised product is available hospital exemptions would no longer be allowed unless there are supply issues impacting the clinical outcomes for patients or clear demonstration of benefit over the approved product. It is worth pointing out the recent European Commission v Republic of Poland (case C-185/10) at this point where the Court of Justice of the European Union confirmed the supply of unlicensed medicines cannot be justified solely on the basis of cost.