



ABPI response to European Commission consultation on advanced therapy medicinal products

28 March 2013

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Introduction

The Association of the British Pharmaceutical Industry (ABPI) represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in the UK.

Our industry, a major contributor to the economy of the UK, brings life-saving and life enhancing medicines to patients. Our members supply 90 per cent of all medicines used by the NHS, and are researching and developing over two-thirds of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases.

The ABPI is recognised by government as the industry body negotiating on behalf of the branded pharmaceutical industry, for statutory consultation requirements including the pricing scheme for medicines in the UK.

We welcome the opportunity to contribute to the European Commission consultation on advanced therapy medicinal products (ATMP) regulation 1394/2007 (the ATMP regulation).

General points

For Europe to stay ahead in the development of ATMPs it will be important to ensure a well networked community, including academia, industry, regulators and manufacturers working together in pursuit of common objectives.

The European regulatory framework has helped to build and maintain public support for this field enabling ethical exploration of a broad range of potential ATMP.

Some of the key challenges in developing new therapies include:

- The high and increasing costs and risks of bringing new medicines and therapies to the market;
- Recognising, valuing and rewarding innovation appropriately, which are critical to industry's ability to sustain long term investment in R&D that will deliver new medicines in the future;
- As the pharmaceutical industry continues to evolve there is an increasing need for partnerships between industry, academia, healthcare providers, regulators, and medical charities if we are to deliver innovative medicines to patients and improve health outcomes.

Response

The ABPI support the high level messages put forward by the European Biopharmaceutical Enterprises (EBE) in relation to advanced therapy medicinal products which are consistent with that of the European Federation of Pharmaceutical Industries and Associations (EFPIA).



Please provide your comments on the requirements for marketing authorisation applications set out in the Regulation.

The manufacture of advanced therapies is still limited to a relatively small number of manufacturers so the experience base is relatively small. With this proviso, the view is that the ATMP Regulation is generally working satisfactorily. A specific comment noted was that a wide range of products are classified as advanced therapies and more flexibility from the EMA CAT in using assessment methods appropriate for particular products would be welcome.

Appropriate coordination between the CAT and the Committee for Human Medicinal Products (CHMP) in reaching a decision on marketing authorisation is required and should also be addressed.

There is a good deal of duplication in the EU regulatory path and clear guidance, coordinated between EU and Member State levels, is needed from early development to marketing authorisation and up to pricing and reimbursement.

There is considerable flexibility at national level to accommodate the development of advanced therapeutic medicines. Nonetheless, further EU harmonisation of guidance from the regulators and advisory bodies would be helpful to the field.

A review of the preclinical data required for cell-based therapies would be valuable. New models and approaches may be needed to assess the pre-clinical and clinical safety, quality and efficacy of this novel class of therapies.

While clinical development of small molecules and biological products are reasonably well characterised and understood, development of regenerative cell therapies requires a different product development approach. There is therefore a pressing need for connectivity between communities engaged in early stage product development, clinical delivery and evaluation, and manufacturing, as well as with regulatory agencies to explore and understand the complex nature of the clinical development requirements for cell therapies. Shaping a clinical development road map / EU level framework for different therapy options to ensure optimal trial design, product safety and efficacy would be helpful.

Clinical trial design for evaluating regenerative cell therapies poses particular challenges and requires focused attention and development. For example, selection of the clinical indication, appropriate patient population and long-term follow up will require careful consideration and definition.

Despite creation of supportive local tools such as the UK Stem Cell Tool Kit¹, uncertainty remains in both academia and industry on the appropriate regulatory path, particularly where

¹ <http://www.sc-toolkit.ac.uk/home.cfm>



regenerative medicine (RM) extends beyond stem cells. For example, the inherent individuality and uniqueness of some advanced therapy products may require a case-by-case approach in the identification of risk and related mitigation. National activities such as the MHRA Innovation Office will help navigate this landscape in, particularly for UK SME's and is a welcome step in the right direction² but additional support is needed at EU level too.

Considerations of appropriate patient number and requirement for placebo-controlled trials may need to be re-examined for ATMPs across all phases of clinical development.

- **Recommendation:** Joint workshops, for academia and industry, on the regulatory framework for ATMP are needed to continue to improve our understanding of important principles as experience is gained.
- **Recommendation:** Research funders and regulators should establish a clinical development road map, facilitated by initial knowledge exchange between experienced developers, based on proposed best practice to gain marketing approval.
- **Recommendation:** Regulators to engage with industry and other experts in drafting future regulatory guidelines for ATMPs, including dialogue on the appropriateness of the 'one-size-fits-all' approach in ATMP development.

Please provide your views on whether the procedure foreseen in the Advanced Therapy Regulation to assess compliance with the essential requirements of the medical device legislation is adequate.

The EBE Personalised Medicines Taskforce is developing comments on the revision of the in-vitro diagnostic medical device legislation at an EU level and it has been agreed that any EBE input on the consultation on the ATMP Regulation should be aligned with these comments.

There is the potential for unnecessary complexity in the development of combination ATMP: device products and clear roles for EMA and the Notified Bodies are required to avoid delays and duplication of work and requirements. EU level guidance on this topic would be welcome.

Please provide your views on the authorisation procedure foreseen in the Advanced Therapy Regulation for combined advanced therapy medicinal products.

See responses to above questions.

Please provide your views on the application of the hospital exemption.

² <http://www.mhra.gov.uk/Howweregulate/Innovation/index.htm#2>



Accelerated routes to the patient (hospital exemption and specials) are very useful in the development of these disruptive technologies. However, a key issue is that the requirements at national level are not clear and are not harmonised. The definitions for hospital exemptions are important but are not consistent across Member States which has implications for example in, ensuring that hospital products are manufactured to the same Good Manufacturing Practice (GMP) standards.

Importantly, there is evidence that some Member States are undermining the uptake of an approved ATMP by applying the hospital exemption – see report from the Pharmaceutical Committee in Annex 1.



Pharmaceutical
Committee_Hospital e

This was not the intent of the hospital exemption; it acts as a disincentive to the development of ATMPs in the EU and does not ensure a high and consistent level of protection for patients.

The EBE letter on hospital exemption, attached below and forwarded to DG SANCO in September 2012, will be added by EBE as an annex to the response to the Commission, and is attached for information.



EBE paper on hospital
exemption final.doc

Although we support traceability of ATMPs to link products to patients who receive them as stated in Article 15(2), we do not support Article 15(1) as it is currently written. This is because the text implies that marketing authorisation holders (MAH) should maintain a system to trace all substances that come into contact with tissues and cells, which could potentially include pipette tips and cell culture flasks. We believe that the intention is to ensure traceability for safety and quality monitoring. We request that this text is clarified to reflect its intention.

Please provide your views on the incentives provided for under the Advanced Therapy Regulation.

Following marketing authorisation there are further expenses to be met and these can be particularly onerous for SMEs. These expenses include variations, translations, and post authorisation pharmacovigilance commitments.

Further financial support to help defray these the post authorisation costs would be a very useful incentive.



Adequate funding of projects to stimulate embryonic stem cell research through, for example, Horizon 2020, would be welcome. For information, see the article in Science Business in which stem cell research through Horizon 2020 is briefly mentioned³. Incentives accessible to non-profit organisations should be considered.

Health Technology Appraisal (HTA)

ATMPs may require new and different aspects of value to be taken into account during their evaluation by HTA bodies and payers, and therefore different models may be required to assess value. Early dialogue between stakeholders including government, regulators, HTA bodies, academia and industry should be established to progress these discussions and work to develop an evaluation framework suitable for ATMPs in focused disease areas. The value of such innovative medicines must be recognised; innovative treatments that benefit patients must be used by the Member State health systems and appropriately rewarded if companies are to be encouraged to invest upfront in the development of high-risk ATMP. In addition, the potential market(s) is likely to be niche and small, this coupled with the requirement to demonstrate cost effectiveness and positive health technology assessment outcomes will be important decision making factors. Early and progressive reimbursement would be advantageous.

- **Recommendation:** Joint government, HTA, academic and industry identification of indications of high unmet need to justify cell-based therapy, and framework and criteria for marketing authorisation, for example agreement on “significant improved outcomes” definitions for subsequent application during regulatory and reimbursement reviews.
- **Recommendation:** Advanced therapies may require new and different aspects of value to be taken into account during their evaluation by HTA bodies and payers and different economic models may be required. Early dialogue between stakeholders including government, regulators, HTA bodies and industry should be established to progress these discussions.

Some biopharmaceutical companies are engaged in discovery-stage ATMP projects and some companies are actively investigating tissue regeneration. Within the cell therapy area investment opportunities are seen as high-risk due to the lack of specific data requirements from regulators, the recent uncertainty in Europe around intellectual property (IP) and the patent landscape, and the associated risk in achieving successful short-term return on investments by SMEs to justify continued cash flow by their investors. These collectively impact on investor sentiment.

In order to prepare for these novel therapies it will be important to ensure that a robust health economics framework is developed in parallel to the regulatory framework. Without

³ <http://www.sciencebusiness.net/downloads/Regenerate%20the%20Future.pdf>



this pharmaceutical companies will find it challenging to determine the return on their significant R&D investment.

Please provide your views on the scope of the Regulation and in particular as to whether the scope should be modified to take account of technical progress.

Elements that could be considered to ensure that the scope of the Regulation takes account of technical progress include:

- The impact of HTA-EMA combined scientific advice.
- The problems of conducting clinical trials for ATMPs in orphan indications, including small number of patients and appropriate statistical approaches.

Additional comments

- Harmonisation of associated legislation is required notably for Directives 2004/23/EC and 2006/17/EC, which set standards for quality and safety for human tissues and cells intended for human applications.
- Global harmonisation between different regulatory jurisdictions covering the EMA and FDA but also Health Canada, Asian authorities and, in the longer term, with ICH is desirable. There are contacts between EMA and FDA to discuss advanced therapies and from an industry perspective it would be useful to know what issues are being discussed and have the possibility to provide input (e.g. via a stakeholder meeting).

Public and patient engagement

As in all emerging areas of science, it is vitally important that patients clearly understand the risks and benefits of cell based therapies. Activity by UK initiatives such as Sciencewise⁴ and organisations such as the International Society for Stem Cell Research⁵ are valuable in facilitating public engagement with the issues, and the latter in helping and supporting patients in making informed decisions.

The ABPI would like to thank the European Commission for the opportunity to contribute to this consultation and would be happy to answer any questions on the specific feedback provided.

⁴ <http://www.sciencewise-erc.org.uk/>

⁵ <http://www.isscr.org/>