

## ***EuropaBio Position on Advanced Therapy Medicinal Products\****

### ***March 2013***

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## **1 Introduction**

Further to the European Commission’s invitation to EuropaBio to provide input regarding the implementation of the Advanced Therapy Medicinal Products (ATMP) Regulation (EC/1394/2007) (“the Regulation”) as part of a wider Commission analysis on the Regulation, EuropaBio conducted a survey that aimed to gauge and gather the views of, and issues confronted by, members who are active in the field of ATMP development in Europe.

The implementation of the Regulation gave companies high hopes that it would facilitate the opening up of the European market to innovative new ATMP products. However, currently (March 2013), only two ATMP Marketing Authorisations (MA) have been granted out of a limited set of applications to the European Medicines Agency (EMA). In addition, the results of a recent EUDRACT analysis showed that the majority of ATMP development projects are currently still in Phase I/II (*Molecular Therapy, vol 20, March 2012, 479-482*). This observation was also confirmed in the EuropaBio survey.

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\* ATMPs

Though the development stage of most ATMPs might still be premature for MA application, EuropaBio was interested to ascertain, identify and understand the underlying causes and whether the Regulation itself has been the reason why these hopes have not yet been fully realised or whether the issue lies more in the various interpretations of The Regulation by EU Member States (EU-MS).

This paper summarises the viewpoints and experiences of EuropaBio ATMP member companies, derived from their responses to the survey.

## **2 Overall assessment of Regulation EC/1394/2007**

In general, EuropaBio is of the opinion that the Regulation has been an improvement in terms of better defining and regulating ATMPs in Europe. There has been much greater clarity regarding the legal and development framework for ATMPs, the move towards the harmonisation of legislation across the European Union (EU) and the facilitation of increasing standards and overall quality in the regulatory environment.

Difficulties continue to be encountered particularly with some of the requirements of the Regulation, due either to its practical implementation, and/or to differences in interpretations and implementation at national level.

However, we do not believe that a recast or review of the current Regulation is required. Instead, a series of improvements would be advisable to further facilitate and stimulate development of ATMPs in Europe. It is essential that the complexities of administrative burdens are not increased by the Regulation, whilst continuing to facilitate and simplify the development of innovative medicines for all developers, including SMEs.

### ***2.1 Difficulties inherent to the requirements of the Regulation and its implementation at European level***

The limited time frame set by the Transition Period (TP) is one of the hurdles that companies developing ATMPs have to face. As a matter of fact, the TP set by the Regulation was very restrictive in preparing the data for long-term efficacy and safety and also did not take into account in a practical manner that ATMPs have been available on the market for many years. The variety of requirements in various EU-MS prior to the passing of the Regulation also contributed to the fact that the TP was just too short for cross-border EU harmonisation to take place.

EuropaBio acknowledges the paramount role played by European regulatory stakeholders and hopes that a favourable science and data-driven environment fosters meaningful and trustworthy Public Health outputs. This effort should preferably encompass the whole lifecycle of ATMPs (i.e. at the pre-registration, registration and post-registration steps).

On the one hand, it is felt that the guidelines issued by the EMA's Committee for Advanced Therapies (CAT) contain gaps and imprecisions leading to misunderstandings. For instance, in addition to the general comments on biological products, further guidance on quality data filing requirements would be welcomed to more adequately reflect the expected information for cell and gene therapies in the eCTD structure.

EuropaBio acknowledges the efforts of the EMA's CAT to engage in a constructive dialogue with stakeholders in order to foster a better environment for the development of ATMPs. Such efforts need to be emphasised in order to maintain and promote further development of such ATMP-specific interactions and establish relevant mechanisms in order to increase the predictability of a positive outcome of the development plans and the acceptance of the clinical data thereof.

EuropaBio would welcome further streamlining of the scientific review process by the different EMA committees such as the CAT and CHMP. EuropaBio feels that this would be best achieved by increased dialogue between these committees, in order to clarify requirements and reduce uncertainties for ATMP developers.

EuropaBio is eager to take part in any activities which would further strengthen these links and to promote any efforts to clarify the ATMPs lifecycle framework.

## ***2.2 Discrepancies in the national implementation of some of the ATMP Regulation requirements***

The ATMP Regulation refers to certain provisions that require the definition of specific conditions and/or execution control by EU-MS.

EuropaBio considers that there are wide discrepancies between member states regarding the national implementation of the legislation. The most notable example is how EU-MS have interpreted and implemented products falling under the hospital exemption (see dedicated section below).

Other areas of discrepancies among EU-MS also exist, including:

- Differing interpretations of legal products on the market and of the application of the Regulation's transition period.
- Differing scientific approaches on aspects for which the Regulation refers to other existing frameworks, such as clinical trial assessments, access to use of starting materials (human cells and tissues), GMO-related frameworks and a lack of harmonisation surrounding GMP certifications. Although none of these aspects are directly linked to the Centralised Procedure for ATMP MA, the highly fragmented national and/or local approaches do hamper its development and market access. In this context it also needs to be recognised that local ATMP expertise remains fairly limited, as this was one of the main reasons for the establishment of the CAT scientific committee. EuropaBio advocates for the need of a two-way interaction between the relevant stakeholders (i.e.; **Top Down:** CAT to national-specific stakeholders (National Competent Authorities, Ethics Committees, Specific bodies dealing with ATMPs) with both training and follow-ups, **Bottom Up:** Practical experience fed into the "concepts" with appropriate interactions and follow-ups). Further (legal) harmonisation of the clinical trials, cells and tissues directive requirements and GMP inspection alignment would be welcomed to obtain greater predictability and reduce complexity, a key requirement for likely investors.

### 2.2.1 The specific issue of Hospital Exemption:

Article 28 of The Regulation foresees the exclusion of some ATMPs from its scope and requires national procedures to regulate these products, referred to as ‘Hospital Exemption’ (HE). These products have been referred to in the Regulation as *“ATMPs prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient”*.

There has been a major lack of harmonisation in defining HE in the EU-MS. Some member states, have not even implemented the HE yet. In particular, some EU-MS have used different definitions for the use of ‘non-routine’, whilst others have not defined it at all. As a consequence, there are major irregularities in the national implementation of HE as reflected by the different interpretations of ‘non-routine’.

In addition, the regulatory environment for products developed under HE is not equivalent to the one for ATMPs developed within the Regulation/Medicines Legislative framework. The need for documentation for effectiveness and safety, the dossier requirements and the actual authorisation process and control of requirements by the national regulatory authorities, are believed to be much simpler and at a lower standard than for those for ATMPs falling under the scope of the Regulation, but also vary widely in the different EU-MS.

Whilst EuropaBio acknowledges the need for allowing patients in specific situations to receive custom-made products, such as in very rare conditions and when no other equivalent alternatives are available, HE products remain largely experimental in nature and lack the systematic development process and robust assessment of safety and efficacy that medicinal products have to undertake. Generally, there is a lack of clinical proof of the safety, efficacy and efficiency of products used under the HE scheme. Therefore, in the interest of Public Health and of patients, EuropaBio believes that the HE should only be restricted to situations where no alternative options exist. These options could be either MA granted to an ATMP to treat a similar condition or patient’s enrolment in clinical trials with ATMPs approved by national regulatory authorities and addressing the same condition. Moreover, in order to best serve Public Health and information given to EU citizens and irrespective of the size of the HE audience/recipients, EuropaBio advocates that the development of HE be subject to an adequate vigilance system shared between the European Commission and EU-MS allowing for a “post-administration” follow-up with adequate reporting. Such an approach would increase the cooperation between EU-MS on aspects related to the coordination and the traceability of the use of those ATMPs (such as in the context of clinical trials, as referred to in the letter sent by EuropaBio to the European Commission in January 2012 regarding this subject).<sup>†</sup>

Providing further guidance and ensuring that the EU-MS comply with this general principle would protect Public Health and the patient’s best interests and safeguard ATMP developers’ incentive to develop new ATMPs by ensuring that once approved, their ATMP will not suffer from undue competition with HE products.

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<sup>†</sup> Letter from EuropaBio to the European Commission, DG SANCO, Directorate D, on 11 January 2012, re: ‘Update on the EU, national and regional authorities in charge of the review and approval processes for clinical trials using Advanced Therapy Medicinal Products’

## 2.2.2 Biobanks, Access to Tissue & Cells & the Tissue & Cells Directive

In order to develop and produce ATMPs, developers need to get access to the starting material, (i.e. human tissues and cells). A large part of the requirements for ATMPs are hence actually derived from the Cells and Tissue Directive (2004/23/EC) in addition to the Regulation. There have been wide differences in implementation of the directive across Europe, which complicates access to the starting materials for ATMPs.

EuropaBio is of the opinion that it would be highly beneficial to reassess the Tissue & Cells Directive in order to review and harmonise its implementation in the different Member States, but also to clarify and streamline the interactions between the Tissue and Cells Directive and the ATMP Regulation.

Comments from our survey regarding the Directive to emphasise this point included:

- *“More harmonisation of rules and definition would be helpful – for example, the access to products from biobanks is particularly complicated in Germany, as they are regulated at the state level rather than the federal level and in Belgium, the [Tissue & Cells] Directive has been implemented through creating different structures [...] and introduced differences as to whether or not the ATMPs to be produced are intended for autologous or allogenic use”*
- *“It’s difficult to obtain research test material [...] and different national/local interpretations to control the Tissues & Cells framework require different national/regional approaches resulting in an increased administrative burden.”*

One could consider changing the legislative instrument from a Directive to a Regulation to maximise harmonisation across all EU-MS.

## 2.3 HTA Requirements

Even though not strictly related to the ATMP regulatory environment (i.e. the ATMP Regulation, the Medicinal Products Directive, or the Directives on Cells and Tissues requirements) EuropaBio would also like to point out that the national and/or regional requirements for market access, and more specifically Health Technology Assessment (HTA) requirements are challenging and constitute a major hurdle for the successful market entry of ATMPs, particularly so where the MA holder is an SME.

ATMPs are highly innovative products that have the potential to dramatically change medical practices. The level of requirements and additional evidence requested by HTA agencies, particularly for highly innovative products, often goes beyond the data available at the time of MA and prevent the centrally approved ATMP from being rapidly introduced to the market on an EU-wide basis.

In addition, ATMPs often involve new and resource-intensive technologies that bear a cost. Moreover, in times of financial crisis, the penetration of ATMPs to the market is challenged by two combined synergistic factors: on the one hand, the perception that ATMPs are expensive and not cost-effective, and on the other hand, a lower willingness to pay for such breakthrough technologies. Consequently, there could be a situation that will develop where their use would be restricted to patient sub-groups within the approved indication.

Finally, there is often a wide heterogeneity of the HTA assessments as well as the medical practices and modalities across countries prior to the ATMP's introduction. Since HTA implies a comparative assessment of the ATMP with such current practices, the prominent lack of standardisation in the field of ATMPs may potentially lead to different and divergent outcomes.

EuropaBio advocates for a more consistent, predictable, open and flexible approach of HTA agencies towards ATMPs that would provide companies with the opportunity to more easily and rapidly launch their product onto the market in order to increase knowledge and experience on their use in real medical practice.

## **2.4 SME and Development Incentives**

The aforementioned hurdles or difficulties are common to all ATMP companies but they are particularly significant to Small Medium Enterprises (SMEs) which have much more limited resources and time to address them. In view of all the above, EuropaBio calls for maintenance and a reinforcement of incentives for ATMPs, SMEs and access to finance by SMEs engaged in ATMP development. Currently, most ATMPs are developed by SMEs which often lack capital to fund extensive clinical research to support marketing authorisation. Phase III studies specifically are difficult to finance.

These HTA-related hurdles and the lack of finance for SMEs are interconnected. Indeed the difficulties of HTA assessment and market access are now more and more acknowledged by investors who prove to be more reluctant to invest in ATMP-developing companies since their highly innovative technologies and treatment strategies are often perceived as riskier than of products using well-established and widely spread technologies. This reluctance to invest in these cutting-edge technologies is not so much related to the risks associated to the technology or the product's intrinsic potential, but because of doubts in the possibility for the SME to effectively get coverage and market access for the product both across the ICH region (i.e.; Europe, Japan, United States of America) and other countries.

## **3 Recommendations and Conclusion**

EuropaBio is of the opinion that the ATMP Regulation has been a major advancement in encouraging the development and approval of ATMPs in Europe.

It has not been sufficient however to result in a surge of newly-approved ATMPs in the five years since it entered into force, even though the number of companies active in ATMP development in Europe and investment in such companies has significantly increased over these corresponding five years. This is thought to be due on the one hand, to specific issues encountered during the development of these highly promising and complex new technologies and its human applications, and on the other hand, to some hurdles lying with the adequacy of the regulatory framework. Difficulties have indeed been reported in the way the Regulation has been divergently implemented at European and EU-Member States (EU-MS) level and between EU-MS themselves. This is also exemplified by the very diverse implementation of the Cells and Tissue Directive across Europe.

All of the suggested improvements for further streamlining and clarifying the ATMP framework would greatly benefit any developer and more specifically, having to cope with this framework

should not be seen as a resource consuming activity for SMEs. Therefore, it should not divert resources from innovation.

Going forward, EuropaBio recommends:

- From the legislative/regulatory framework perspective:
  - Not to review the ATMP Regulation in its entirety but to rather review some of the elements of its practical implementation:
    - Ensure a flexible interpretation of guidelines in order to be able to take the latest scientific advances into account. New guidelines should always be aligned and specific.
    - Further clarify and strengthen the definition of Hospital Exemption, so that it is only implemented in limited situations where no alternatives exist, such as when there are no ATMPs to treat a similar condition approved or when enrolment in clinical trials with ATMPs approved by national regulatory authorities and addressing the same condition is not possible.
  - Review, clarify and streamline the interactions of the ATMP Regulation with the Cells and Tissue Directive. Consider changing the legislative instrument for Cells and Tissue from a Directive to a Regulation to maximise harmonisation across all EU-MS.
- To Acknowledge and emphasize the paramount role of the Committee for Advanced Therapies (CAT) in order to foster an environment which improves the certainty of the regulatory pathway and the possibility of a positive outcome of ATMPs development/clinical plans leading to a Marketing Authorisation (MA). In order to facilitate the translation of research into commercial products, the following aspects should be taken into account:
  - Scientific advice: Encourage the communication between the CAT and the relevant national stakeholders in order to increase knowledge sharing.
  - Improve the harmonisation of the ATMP clinical trials review and approval processes by ensuring similar approaches in the use of starting materials and the harmonisation of GMP certifications.
- Confirm the CAT's prominent role in the MA process within the CHMP's review process.
- To address the impact of the different HTA processes and requirements. This specific issue may significantly hamper ATMP developers, especially SMEs, to successfully raise the funds required to foster their further development and growth (i.e. carry out large clinical studies, launch and market ATMP products in a timely fashion across the EU and reach out to the Global Market).
- To acknowledge the difficult economic situation, to maintain and reinforce incentives to ATMP development and SMEs and, in particular, to assist in access to finance for SMEs.

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