Co-ACT response to the European Commission's invitation to submit comments as part of the public consultation on Regulation 1394/2007 ("ATMP Regulation")

Co-ACT welcomes the initiative of the European Commission and is happy to provide comments on the consultation topics launched by the Directorate General for Health and Consumers relating to Regulation 1394/2007 ("ATMP Regulation").

About Co-ACT:

Co-ACT is an association grouping together the main biopharmaceutical companies established in Belgium developing Advanced Therapy Medicinal Products (ATMPs).
The objective of Co-ACT is to protect and stimulate the R&D activities, production and export activities in order to consolidate Belgium's status as an investment location for ATMP companies.
Its members include Beta-Cell, Bone Therapeutics, Cardio3 BioSciences, Promethera Biosciences, and TiGenix. All these companies are Small and Medium-sized Enterprises (SMEs).

The very first Advanced Therapy Medicinal Product approved in Europe following the requirements of the regulation 1394/2007 is from TiGenix (ChondroCelect®) and is still to date the only one on the market.

Co-ACT companies are members of Belgian and/or European biotech associations such as bio.be, pharma.be, EuropaBio and/or EBE. Co-ACT largely shares their views and supports their comments.

1. Marketing authorization application requirements for advanced therapy medicinal products

Co-ACT believes that the ATMP Regulation has been a major milestone and advance for companies developing ATMPs: the regulation has enabled a more adapted and clearer legal framework that takes into account specificities of ATMPs, has allowed more harmonisation across the European Union and has thereby contributed to facilitate ATMP development.

Areas of potential improvements relate to the practical implementation of the ATMP Regulation, in particular through the amendments of Directive 2001/83/EC and annexes ("Community Code"), and enhancing harmonisation of implementation at national level by eliminating or limiting differences of interpretation.

Co-ACT does not believe that a full recast or review of the current ATMP Regulation is required.

A review of some of the requirements in the Community Code - in particular its annexes that relate to ATMPs - would be very valuable. Some of the requirements in annex I are not optimally adapted to ATMPs such as those relating to reference standards or potency assays for instance. A thorough review of these requirements in collaboration with the Committee for Advanced Therapies (CAT) and with input from ATMP companies would be welcome in order to better take into account the specificities of ATMPs.

The guidelines issued by the EMA's Committee for Advanced Therapies (CAT) contain gaps and imprecisions leading to misunderstandings. For instance, further guidance on the quality data filing

requirements would be welcomed to more adequately reflect the expected information for cell and gene therapies in the eCTD structure.

In addition, other existing frameworks such as clinical trial assessments, GMP requirements or access to starting materials (i.e. human cells and tissues) have a direct impact on ATMP developments and do pose a number of specific challenges.

With respect to clinical trials, the assessment of applications being carried out at national level, there are wide variations in interpretation, as well as ATMP expertise and know-how in the different countries, leading to a wide variation of requirements in member states. The requirements to demonstrate viral safety of cells and tissue from donors is a good example of the wide variety of requirements in Europe. The highly fragmented national approaches hamper the development and market access of ATMPs. National authorities should also be encouraged to take a more flexible approach when they review clinical trials applications for ATMPs, particularly when such trials have already been authorized in other countries of the European Union. The divergence of opinions and the accumulation of specific requests are particularly harmful to development of ATMPs by SMEs who need to run multinational studies with limited resources and presence in the different countries. Co-ACT believes that enhanced interactions between the CAT and national authorities would be beneficial in order to harmonize requirements and streamline the assessment process in the different countries.
Similarly more harmonization would be required around GMP certifications across Europe. An additional possible improvement would be to adapt GMP requirements for phase I clinical studies, in line with the approach taken by the US authorities.
Generally, Co-ACT acknowledges the positive role of CAT and would welcome further interactions between CAT and ATMP companies during the product development and throughout the product lifecycle in order to increase mutual understanding of requirements and the predictability of a positive outcome during the marketing authorization process.

Because tissues and cells are starting materials in ATMP development and production, a large part of the requirements for ATMPs are defined in Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells ("Cells and Tissue Directive"). There are wide differences in implementation of the Cells and Tissue Directive across Europe and several countries have imposed national requirements going much beyond those defined in the directive.

A specific difficulty for Co-ACT companies is the complex transposition of the Cells and Tissue Directive in Belgium: the Belgian law defines different requirements with different types of authorizations and processes depending on whether the ATMP is for autologous or for allogenic use. Under the Belgian framework, producers of allogenic ATMPs are totally reliant on authorized hospital tissue banks for the sourcing, the control and testing of human cells and tissues which are needed to manufacture their products whilst these hospitals have no incentive to develop these services. As these limitations and complexities, leading to legal uncertainties in some cases, do not exist in surrounding countries, companies in Belgium experience more difficulties to establish their manufacturing facilities in Belgium.

Co-ACT is of the opinion that greater harmonisation, in particular with regard to the Cells and Tissue Directive is required and would like the Commission to consider changing the Directive into a Regulation to this aim.

Enhanced harmonisation of requirements, simplification and limitation of administrative burdens are all essential to the survival and growth of SMEs.

2. Requirements for combined advanced therapy medicinal products

Co-ACT companies do not have the experience of a marketing authorization process for combined ATMPs and have therefore no specific comments on the particular requirements for these.

3. Hospital exemption

The hospital exemption, as defined by article 28 of the ATMP Regulation needed to be transposed in national legislations. Five years after publication of the ATMP Regulation, we see a great variability in this implementation. In particular the notion of 'non routine' preparation has led to different interpretations: some countries mention a maximum of preparations per year (Netherlands); others adopt a case-by-case approach (UK); others accept the routine production provided that variations in the procedure are applied on the basis of medical justification for each patient (Germany); finally some countries have still not published a legal text to transpose these requirements (Belgium).

Co-ACT fully acknowledges the legitimate need to authorize hospital exemption products, tailor-made to respond to specific needs such as in very rare diseases and when no alternative is available. However, products under hospital exemptions remain largely experimental by their nature and do not undergo the rigorous and controlled development and assessment of their quality, safety and efficacy which are applied to any new medicinal product.

Therefore in the interest of patients and public health, Co-ACT believes that the hospital exemption needs to be limited to situations where no alternative exists. ATMPs duly authorized in similar clinical conditions or the enrolment of patients in duly authorized clinical trials for similar conditions could constitute such alternatives justifying a rejection of the hospital exemption status.

A too permissive interpretation of hospital exemption would go against the interests of patients in the medium to long-term for the above mentioned reasons, but could also be detrimental to the development and investments in the ATMP sector. Indeed should hospital exemption be possible when authorized products or authorized clinical trials exist for the same clinical conditions, this would constitute undue competition which would limit the attractiveness for investors and would seriously jeopardize the optimal development of these breakthrough therapies.

Finally the absence of a clear and specific regulatory framework to secure the use of hospital exemption products creates a legal uncertainty which in turn is also detrimental to the investments and development of this sector.

Co-ACT pleads for a more specific definition of hospital exemption (e.g. the notion of 'non routine' could be strengthened), for further guidance on the requirements for hospital exemption products and for an effective transposition into national legislations with the objective to foster public health, protect patient's best interests and safety, and safeguard ATMP developer's incentive to develop ATMPs.

4. Incentives for the development of advanced therapy medicinal products

ATMPs use highly innovative technologies and offer the potential of breakthrough treatments. The difficulties associated with ATMP development are common to all companies developing them but are particularly significant to SMEs which typically lack resources and time to address them.
Co-ACT calls for the maintenance and 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, typically the phase III studies, to support marketing authorization.

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 Marketing Authorisation (MA) holder is an SME.
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 a 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.

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.
Along with EuropaBio, Co-ACT 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.

These HTA-related hurdles and the lack of finance for SMEs are interconnected. Indeed the difficulties of HTA assessment and market access are now better recognized by investors who become 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. Investors express doubts on the possibility to get effective coverage and market access that would allow them to recoup their investments.
Market access difficulties constitute one of the major reasons why European SMEs have to sell their technology or enter into agreement with other bigger companies short before or after marketing authorization.

5. Scope and adaptation to technical progress

ATMP development use cutting-edge technology and is a rapidly evolving field. It is therefore of paramount importance that the regulators take this into account and adopt flexible approaches and enhanced dialogue with ATMP developers.

In this respect, Co-ACT fully endorses EuropaBio recommendations which are the following:

- 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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