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Summary of the 5th annual regulatory conference organised by EBE, in collaboration with the European Medicines Agency (EMA) "Optimising the development of ATMPs to meet patient needs" – London, 16th December 2016

BACKGROUND

Advanced Therapy Medicinal Products (ATMPs)¹ have the potential to be transformative medicines. Nearly a decade after Regulation (EC) No 1394/2007 came into force to speed up patient access to ATMPs, real progress has been made. However, a range of issues, from a lack of sustainable funding models to insufficient transparency and regulatory guidance for biopharmaceutical companies, is still challenging greater uptake of these innovative treatments. The fifth in the series of annual conferences jointly organised by European Biopharmaceutical Enterprises (EBE) and the European Medicines Agency (EMA), held in London, UK, on 16 December 2016, set out the latest progress, identified the remaining critical issues, and discussed a range of potential solutions with members of all stakeholder groups, including patients, clinicians, payers, regulators, academia, industry and investors. Agenda and presentations are available on the [EMA website](#) on the 'Documents' tab for the event and on the [EBE website](#).

INTRODUCTION

Guido Rasi, EMA Executive Director, outlined progress in the past year: EMA's new **PRIME (priority medicines) initiative**² recommended 14 products as eligible for PRIME, 7 of which were ATMPs. EMA is also pressing for **new ways to design clinical trials** including earlier collaboration with payers. "What matters is not only that we approve medicines but that they reach the patients", he said. Critical issues remain, he warned, over how ATMP clinical trial evidence is generated, evaluated and validated, and how big data can be deployed more widely, effectively and safely. The patients' perspective must be at the forefront and directly involved so that we understand and address their needs, he commented.

Andrea Chiesi, EBE Vice-President, noted that while there had been 8 authorisations, 3 had been withdrawn, so "we need to do much more – we can and should improve." He called for **more transparency on all ATMPs** sold in the EU, not only centrally authorised ones, so patients and the public can find information online more easily, and for **timely scientific advice for all biopharma companies**, small and large.. In his view, however, it was of critical importance to find **better sustainability models for ATMPs**. "Things cannot continue in the same way with costs and prices continually increasing", he concluded.

KEY STAKEHOLDER PERSPECTIVES AND INITIATIVES

Regulators

EMA: Since 2009, EMA has been informed of about 500 clinical trials with ATMPs, issued 230 ATMP product classifications, received 215 scientific advice requests, and reviewed 15 applications for marketing authorisation resulting in 8 approved ATMPs. EMA actively engages to support the development of and patient access to ATMPs and has identified actions for implementation within the EMA in 2017; the publication of an action plan is expected in early 2017. Its Committee for Advanced Therapies (CAT) is currently developing or revising a number of guidance documents. Applicable to all

¹ ATMPs comprise gene therapies, tissue-engineered products and somatic cell therapies, derived from a wider range of biological materials, such as cells, tissues or viral vectors. *Source: [EMA report 345874/2016](#)*

² PRIME is a scheme launched by the EMA to enhance support for the development of medicines that target an unmet medical need, through enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier.



ATMPs, guidance on investigational ATMPs covering quality, non-clinical and clinical aspects is expected at the end of March 2017. The guidance on gene therapy medicinal products (GTMPs) addressing quality, non-clinical and clinical aspects for these specific products is being revised with the requirements of SMEs and academia in mind, and also taking into account guidance from other agencies (eg FDA, Health Canada). It is applicable to all GTMPs, but mostly focuses on viral and nucleic acid vectors, although bacterial vectors are included. The quality guidance has an extensive section on development genetics and vector considerations. Release for consultation is expected in the first quarter of 2017.

FDA: The US Food and Drug Administration (FDA) has a 2-armed approach to optimising the development and availability of ATMPs to meet patient needs: **Expedited programmes**, which include priority review designation, accelerated approval, fast track designation, and breakthrough therapy designation (BTD), aiming to expedite approval; and **Expanded access**, for the use of investigational drugs to treat patients with a serious or immediately life-threatening illness or condition, where there is no comparable or satisfactory alternative therapy, and where the potential benefit justifies the potential risks of the treatment (risks that are not unreasonable in view of the disease/condition being treated). Statistics on ATMPs requests granted by the FDA were **presented** per product type. The main reasons for approval rejection, however, included a too small sample size, lack of appropriate control, post-hoc analyses of failed studies, and insufficient evidence that the improvement is 'substantial'.

National Competent Authorities: In France, the independent **Haut Conseil des Biotechnologies** (HCB) combines a Scientific Committee (SC) and an Economic, Ethical and Social Committee (EESC) for a rounded stakeholder assessment. For approval of gene therapy ATMPs, the SC initially evaluates contained use and the risk of deliberate release. If deliberate release exists, both committees contribute. In Germany, the **Paul-Ehrlich-Institut** reported no delays for approval of clinical trials with GMO-based ATMPs due to environmental risk assessment (ERA) evaluation, nor rejections of clinical trials with GMO-based ATMPs due to unjustifiable harmful effects on the health of third persons or the environment, even though decisions are taken in consultation with the Federal Office for Consumer Protection and Food Safety, the competent federal authority for the deliberate release of GMOs.

Patients

Primary immunodeficiency diseases (PIDs) encompass more than 300 genetic disorders and are a very promising area for AMTPs, specifically gene therapy. However, patients called for **more experts** and **centres of expertise across Europe, physician cooperation, confidence to participate, cross-border regulation implementation** and the **involvement of relevant patient organisations**. To improve patient access to ATMPs, 3 steps are vital: increased interaction between stakeholders, consultation, and inclusion. In the development of medicines "patients are not a trial subject or an end consumer, but a partner and true stakeholder."

Industry

Development and manufacturing challenges: using the example of an ex vivo autologous cell and gene therapy product and of a centralised facility versus decentralised, regional manufacturing hubs, where more processes can be automated while maintaining quality and robustness, 3 critical challenges were discussed: **vector scale-up**, moving from adherent culture (small batch sizes) to fully disposable and scalable suspension platforms, eliminating the need for ongoing plasmid manufacture; **ex vivo cell processing**, currently a manual process (extraction) requiring highly skilled operators, where scale-out needs are significant, since patient populations, particularly in oncology, can be large; and **change management and comparability** for manufacturing changes aiming to enable the treatment of larger populations. Key questions arising from the discussed example included agreeing what and how to measure (changes, cycles, processes), how a change in one process will affect (an)other(s), the need for in vivo comparability studies, how robustness can be compared between sites, understanding the variability of cells (inherent in people) and its impact, and analytics and methodologies.

Environmental Risk Assessment (ERA) for EU clinical trials with GMO-based ATMPs: While the Clinical Trial Regulation, due to be implemented in October 2018, will harmonise clinical trial

applications across EU, it does not address ERAs for investigational medicinal products. The preferred options for industry for resolving challenges resulting from different implementation across the EU Member States are having a co-ordinated ERA with one dossier via one central point, as for marketing authorisation applications, or as a minimum, having a harmonised data template, procedures and timings across Member States.

AMTP success story: An autologous ex vivo gene therapy for rare genetic disorders has been developed in partnership with the Italian Fondazione Telethon and Ospedale San Raffaele, acting through their joint Telethon Institute for Gene Therapy (TIGET). Children suffering from ADA-SCID (severe combined immunodeficiencies) normally die before they are 2 years-old, but 100% of the children treated survived after a median follow-up 7 years after having the therapy.

Registries: Patient or treatment registries offer opportunities to generate new data, for label expansion, and to study changes in mode of use or administration, which is particularly useful for ATMPs. However, the **dichotomy between academic registries** (concerned with data quality and integrity, GCP compliance, regulatory accountability and pharmacovigilance) and **industry registries** (concerned with the commitment of investigators, duplications, multiple investigations and questions of independence) makes their use difficult. Other challenges include **implementing clinical trial standards** (a registry is a living creature so data change with the patient's health journey), **study complexity; country or site activation; and restricted access and reimbursement based on payment by result.** A solution could be to have different types of platforms for registries in the hands of **specialised data platform providers** (guardians), with **patients owning the data** (users) and other **stakeholders having access.**

Funding

IMI2 (2014-2024): The second stage of the public-private partnership (*50% EU funding, 50% industry*) [Innovative Medicines Initiative](#) has €3.3bn to allocate. Funding is targeted at **innovative medicines, clinical trial design, patient-tailored adherence programmes, and target and biomarker identification** (safety and efficacy). There are 5 potential IMI2 topics under consideration for ATMPs: **Precision Genome Editing (PGE), clinical development and patient access, clinical development of cell therapies in cancer** (all prioritised for development in 2017), as well as **manufacturing, and immunogenicity.** Initiatives such as the **European Lead Factory**, where 7 companies are sharing 50,000 of their compounds in a shared chemical library to be used by SMEs for target identification and development, was highlighted as "an opportunity to transform the ATMP landscape" as SMEs can use European Lead Factory resources for free. IMI2's newest and largest multi-stakeholder project is **HARMONY**, which aims to improve outcomes in haematologic malignancies.

Venture capital: Investors provided over \$80bn of available venture capital in 2016 (year to date) and €100bn in 2015, far more than individual pharmaceutical and biopharmaceutical companies. Only a tiny percentage of deal proposals are successful each year, however, due mainly to insufficiently novel products being offered, or failure to adequately address an unmet need. The biggest problem for promising start-ups is the **lack of venture capital funding in Europe.** While they often receive initial support, they **lack follow-up finance for the next phases**, which means they have to go to the US or elsewhere and Europe fails to reap the benefit.

Healthcare professionals

The real-life experience of carrying out clinical trials with ATMPs in a clinical setting can mean battling **multiple and often ridiculous barriers**, depending on the **different protocols used in different clinical settings and countries.** One example is bio-safety levels (BSL) attributed to an ATMP candidate by competent authorities, which can differ widely within the EU. In the case of Talimogene-Laherparepvec (TVEC) immunotherapy treatment, a BSL2 designation was given in Austria and Germany, but BSL1 in Spain. While BSL2 information is well defined for the laboratory research, there is no available information on its requirements in clinical settings to aid healthcare professionals with their hands-on work with patients. Study start-up was also markedly quicker in countries without BSL2 designation, it was noted.

Payers

There is no single payer view as there is no single healthcare system in the EU. The issue for payers centres on **when should users be involved in risk/benefit discussions?** This is difficult to answer and usually left to the regulators. The key questions for payers are **what are the available alternatives** to this therapy? Are they **better**? Does the therapy have a **benefit that is important to patients?** How do you **measure and evaluate** that? What do they **cost**?

NEXT STEPS

Paula Salmikangas, Chairperson, Committee for Advanced Therapies (CAT), and **Andrea Chiesi**, EBE, summed up the day’s discussions and the key challenges still to be addressed:

1. ATMPs are a fast-moving field with many particularities, which require considerations by both regulators and payers.
2. More funding and investment in ATMPs is needed, not just seed funding, so that promising therapies and products can be developed and deployed sustainably and successfully in Europe.
3. There must be clearer information and communication between and for all stakeholders to foster more awareness, development and uptake of ATMPs.
4. The challenges of how to better address gene therapies within the context of ERAs for GMOs must be tackled urgently to prevent unnecessary delays in clinical trials.
5. How registry data are used needs to be clarified, particularly in the areas of implementing clinical trial standards, the impact of restricted access, and reimbursement based on payment by result.

While multiple initiatives are currently ongoing by regulatory authorities to speed up access to medicines for patients, it will take more coordinated action by all stakeholders to harness their expertise and strengths to make this happen.

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