OPINION

Challenges with advanced therapy medicinal products and how to meet them

The Committee for Advanced Therapies (CAT) and the CAT Scientific Secretariat

Abstract | Advanced therapy medicinal products (ATMPs), which include gene therapy medicinal products, somatic cell therapy medicinal products and tissue-engineered products, are at the cutting edge of innovation and offer a major hope for various diseases for which there are limited or no therapeutic options. They have therefore been subject to considerable interest and debate. Following the European regulation on ATMPs, a consolidated regulatory framework for these innovative medicines has recently been established. Central to this framework is the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA), comprising a multidisciplinary scientific expert committee, representing all EU member states and European Free Trade Association countries, as well as patient and medical associations. In this article, the CAT discusses some of the typical issues raised by developers of ATMPs, and highlights the opportunities for such companies and research groups to approach the EMA and the CAT as a regulatory advisor during development.

Advanced therapy medicinal products (ATMPs) comprise gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products and tissue-engineered products (for legal definitions see BOX 1 and REFS 1,2). They are at the forefront of innovation, offering potential treatment opportunities for diseases that currently have limited or no effective therapeutic options. ATMPs have therefore been subject to considerable interest, but have generated both positive and negative outcomes.

For example, recent publications have suggested that gene therapy for monogenetic diseases could result in long-term beneficial results and may prove to be an effective treatment strategy[3–5]. In addition, cell-based skin substitutes and cartilage products have already been used for more than a decade, and upcoming somatic cell therapy medicinal products and tissue-engineered products might also become efficacious treatment modalities. However, despite their promise and the progress made, ATMPs have sometimes caused clinical problems, which have led to reports in the lay press. For example, although rare, fatalities following gene therapy have been reported, including a lethal systemic inflammatory immune reaction and leukaemia due to insertional oncogenesis[6,7]. Recently, fetal stem cells were reported to cause a brain tumour, suggesting that cell-based medicinal products (CBMPs) also have intrinsic risks that need to be addressed[8].

With the new European regulation on ATMPs[1], a consolidated regulatory framework for these innovative medicines has recently been assembled. Central to this new legislation is the establishment of the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA) in London, UK. The CAT is a multidisciplinary scientific committee of experts representing all member states of the European Union and countries from the European Economic Area and the European Free Trade Association (Iceland and Norway are currently represented in the CAT), as well as representatives from patient and medical associations (BOX 2). This independent committee, with a high degree of expertise in both the scientific and regulatory aspects of ATMPs, started its work in January 2009. The CAT gathers dedicated European experts to review the quality, safety and efficacy of ATMPs according to standards established by regulatory authorities, and to debate scientific developments in the field. Information on the declared scientific expertise of the CAT members and alternates (reflecting the expertise required by the regulation on ATMPs) can be found in FIG. 1.

The CAT is responsible for the primary evaluation of ATMP marketing authorization applications (MAAs) for the EMA's Committee for Medicinal Products for Human Use (CHMP). The CAT operates two new regulatory procedures for companies developing ATMPs — the classification procedure and the certification procedure — which are both discussed further below. The CAT aims to foster innovative medicines while maintaining a high standard of regulatory responsibility. Guidance had already been developed by various EMA and CHMP regulatory groups (for example, the Biologics Working Party, the Gene Therapy Working Party or the Cell-based Products Working Party) before the establishment of the CAT, and through the Scientific Advice Working Party. However, the CAT now combines and complements these activities within a single committee to support the development of ATMPs in Europe.

Marketing authorization of ATMPs requires, as for all medicinal products, that the applicant demonstrates that the product is consistently manufactured to a predefined quality, and that it is safe and efficacious in patients. The CAT recognizes that some ATMPs will require new strategies for their development and scientific assessment. For example, the clinical performance of many types of CBMPs strongly depends on the final performance of the cell preparation administered. Success depends on the rigorous control of the manufacturing process and specifications, which has

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Box 1 | **Definitions of advanced therapy medicinal products**

Definitions of advanced therapy medicinal products according to the European pharmaceutical legislation are outlined below and can also be found in REFS 1,2.

Gene therapy medicinal product

A gene therapy medicinal product means a biological medicinal product that has the following characteristics:

- It contains an active substance that contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, adding or deleting a genetic sequence
- Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence
- Gene therapy medicinal products shall not include vaccines against infectious diseases

Somatic cell therapy medicinal product

A somatic cell therapy medicinal product means a biological medicinal product that has the following characteristics:

- Contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor
- Is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues

For the first point, the manipulations listed in Annex I to Regulation (EC) No. 1394/2007, in particular, shall not be considered as substantial manipulations.

Tissue-engineered product

A tissue-engineered product has the following characteristics:

- Contains or consists of engineered cells or tissues
- Is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue
- Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions: the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved
- The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor

For the third point, the manipulations listed in Annex I of Regulation (EC) No. 1394/2007, in particular, shall not be considered as substantial manipulations.

limitations inherent to the complex character of ATMPs. Likewise, in addition to the conventional non-clinical models used to study safety and toxicology, appropriate new models are likely to be required given the limited clinical experience that will be available at the time of MAA. Clinical study concepts are particularly challenging as clinical efficacy or safety might be apparent only after several years, and will require the validation of suitable surrogate end points. It is therefore of utmost importance to consider the regulatory and scientific expertise gained from other biological or biotechnological products, and to take into account the particular needs of ATMPs. Developers of ATMPs are often small companies and academic institutions, which necessitates consideration of their particular challenges and assistance requirements during development.

This article aims to facilitate a scientific dialogue between key stakeholders in the field of ATMPs, including academic groups, hospitals, industry, patient organizations and regulatory bodies across Europe and beyond. The major regulatory challenges observed during assessment of such advanced therapies are discussed. The examples given cannot exhaustively represent the various scientific and regulatory issues that are pertinent to ATMPs. But they will highlight issues that are typically raised by developers in scientific advice requests, in which the CAT will have a strong input, and that will be relevant for numerous products assessed by the CAT. The article also highlights the opportunities that companies developing ATMPs have to approach the EMA and, in particular, the CAT as a regulatory and scientific advisor during development, and learn how they may use the EU regulatory system efficiently.

Cell-based medicinal products

The term CBMPs unites several types of cell therapies — including somatic cell therapy medicinal products and tissue-engineered products — manufactured from viable autologous (patient's own cells), allogeneic (donor cells) or xenogeneic (animal) cells. The cells may also be genetically modified. These products are highly heterogeneous owing to their origin, starting material, degree of *in vitro* manipulation and manufacturing process. This is in addition to cell population type and developmental or differentiation stage (embryonic or adult stem cells, or early committed progenitors, induced pluripotent stem cells, or terminally differentiated cells).

Somatic cell therapy medicinal products are intended to prevent or treat a disease, or to make a diagnosis, by a metabolic, immunological or pharmacological mode of action of the cells (for a legal definition see BOX 1 and REF. 2). Product types falling into this category include cancer immunotherapy products.

Tissue-engineered products are developed for the structural repair of various tissue defects; for example, corneal, heart or liver tissue, blood vessels, cartilage or bone (for legal definition see BOX 1 and REF. 1). The therapeutic intention is to replace the failing tissue with a functionally equivalent tissue structure that preferably persists at the desired location. These types of ATMPs are sometimes associated with structural components that promote the formation of a three-dimensional tissue structure leading to favourable cellular interactions. The active substance in these products might be a functionally immature cell preparation (for example, stem or progenitor cells), or more differentiated cells that form the final tissue (for example, cartilage or skin)[9,10]. The efficacy and safety challenges relating to CBMPs are outlined below.

Patient integration. One of the main challenges of CBMPs is to achieve robust and safe functional and/or structural integration of the product into the patient. In most circumstances, the CBMP should persist in the recipient and should yield a stable therapeutic effect. For instance, CBMPs used for the treatment of degenerative disease should ideally be able to functionally restore or substitute the affected tissue.

However, this is a particularly challenging endeavour as living cells are intrinsically fragile and may be among the most complex pharmaceuticals. Their *in vivo* behaviour depends on their micro-environment and on the interaction between specific receptors

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or cell surface molecules and their respective ligands, which are present either on the CBMP itself or the surrounding tissue (for example, integrins or growth factor receptors). These factors are often species-specific and/or disease-specific, which can complicate efficacy and safety studies in animal models that may not necessarily accurately mimic the human condition. Most importantly, cells are reactive to this environment, that is, they can change their phenotype and migration pattern or other characteristics. Conversely, whenever the environment changes, the cells tend to change accordingly, implying that *in vitro* production will inevitably have an impact on the efficacy and/or safety of any CBMP. The use of growth factors and prolonged *in vitro* cell culture steps may alter the cells in a way that may be difficult to predict without adequate subsequent testing of their behaviour and characteristics. Typically, primary cells do not tolerate long-term *in vitro* culture, often resulting in commitment to apoptosis, which may ultimately have an impact on the actual dose and final clinical outcome when implanted into patients.

In addition, finding appropriate cell markers can be challenging as they are not always specific or directly correlated to cell function. For instance, the marker profiles established for bone-marrow-derived mesenchymal/stromal stem cells (MSCs) may turn out to be less useful for MSCs isolated from other sources, as many of the markers used to define MSCs may also be expressed by other differentiated cell types. Similarly, robust directed differentiation of stem cells (for example, induced pluripotent stem cells or embryonic stem cells) into the desired differentiated cell types is one of the major hurdles that affects the eventual clinical translation of these particular stem-cell-based products. Moreover, this is compounded by the inherent tumorigenic risk of undifferentiated or incompletely differentiated stem cells that would need to be eliminated from the CBMP before administration to the patient[11].

Characterization. Poor definition and control of a product — including during its manufacturing process — may directly affect safety and efficacy. From a regulatory perspective, appropriate characterization of a product is therefore necessary. Although this may sometimes be cumbersome, knowledge of the relevant quality attributes of the final product administered to the patient should be seen as a powerful tool. This is because it will allow for adaptation of the product and will facilitate assessment of the impact of any change in the manufacturing process, which will often be implemented at a later stage of development or even after the marketing authorization has been granted.

The required characterization programme, as a tool for monitoring of consistency, will usually also consider the functional capability of the cells related to the intended clinical use. However, linking specific cell characteristics to the intended function may be the most challenging aspect. For example, for products containing chondrocytes, the manufacturing procedure should be developed and validated to ensure the proliferation and differentiation of chondrocytes, while preventing the possibility of their de-differentiation to form fibrous tissue. Only by these means can efficient cartilage repair with hyaline cartilage (and not fibrous cartilage) be achieved. In this respect, one of the clinical challenges that needs to be addressed is how to measure long-term clinical outcome. The differentiation into the desired tissue type, and thus the functional tissue repair, might take a long time; for example, several years for cartilage or neuronal tissue. This necessitates the conduct of lengthy clinical trials, which will be a financial burden for the, often small, companies developing the product. In addition it may lead to problems such as the maintenance of follow-up visits of patients or complications of results owing to the underlying natural disease course or other co-morbidities. A potential solution could be to provide part of the clinical efficacy results as a post-marketing obligation[12], as long as a satisfactory degree of positive benefit–risk estimation can be demonstrated for the product at the time of the MAA, for example, by validated surrogate markers.

Overcoming efficacy and safety challenges. The complexity, plasticity and fragility of cells with regards to their vitality and their behaviour necessitate the exploration of additional ways for characterization. In addition to assessment of toxicity (such as toxicity related to de-differentiation or loss of cell function, cell transformation and tumorigenicity, or ectopic engraftment in non-target tissues), appropriate non-clinical studies in a relevant animal species can be a powerful tool to also further characterize the cells.

However, finding a relevant animal model may be challenging as, strictly speaking, the only relevant species for testing human cells — when all aspects including receptors, cytokines and micro-environment are considered — is the human being itself, and so any animal model can be expected to have inherent limitations. For example, adult human stem cells for tissue repair grow exponentially and can differentiate into various phenotypes (for example, mesenchymal stem cells to an osteogenic, myogenic, adipogenic or neurogenic phenotype), which will be driven by the respective micro-environment. The toxicology to be expected pertains to two different aspects: the behaviour at the site of injection (for example, de-differentiation or unwanted differentiation), and behaviour at distant sites (for example, after migration to unwanted sites). As cells react in a species-specific manner, nothing might happen upon injection into animals when there is no relevant interaction with animal tissue. Moreover, the animals' immune system will in due course recognize human cells as foreign and thus attack them. This immunogenicity can lead to artificial immunotoxic effects that would not — or to a lesser extent — occur in patients in an autologous setting. Conversely, the rapid elimination of the cells may mask potential adverse events that would occur at a later stage in patients.

However, there are several safety related aspects of manipulated cells that can feasibly only be addressed in animals. These include evaluating biodistribution by invasive techniques or testing the tumorigenic potential with product batches intentionally cultured beyond specifications. Thus, animal studies should be designed with both these limitations and potentials in mind. To overcome these problems, several possibilities can be selected on a case-by-case basis. For instance, the use of immunodeficient animals such as severe combined immunodeficient mice can be used, as these mice will not mount an immune response to the CBMP. However, as the biological systems of human and mouse may not be fully compatible the results may need further verification in other animal species.

One of the most promising possibilities for non-clinical testing is the use of a homologous model. For instance, the use of mouse adult stem cells in mice, which would resemble the CBMP to be used in humans. The advantage here is that all cellular and molecular interactions are supposed to be functional owing to the homologous setting. Nevertheless, the main drawback of this approach is that the medicinal product itself is not being tested. This prevents detection of toxicity arising from potential contaminants in the final product. Sometimes cautious bridging to clinical studies is the only possible option. In such early clinical trials, additional safety measures such as specific safety end points based on theoretical

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Box 2 | **The European Committee for Advanced Therapies**

Members and their alternates, as of February 2010, of the European Committee for Advanced Therapies (CAT) are outlined below. Full details of each member, including contact details, are available from the European Medicines Agency website (see Further information).

- CAT Chairman: Christian K. Schneider
- CAT Vice-Chairperson: Paula Salmikangas
- European Commission representative: María-Angeles Figuerola-Santos
- European Medicines Agency and CAT Scientific Secretariat: Lucia D'Apote
- European Medicines Agency and CAT Secretariat: Olga Oliver-Diaz
- Paul-Ehrlich-Institut and CAT Scientific Secretariat: Isabel Büttel
- European Medicines Agency and CAT Scientific Secretariat: Patrick Celis

Country/Organization	Representative	Alternate
Members nominated from within the Committee for Medicinal Products for Human Use		
Lithuania	Romaldas Mačiulaitis	Jolanta Gulbinovic
Luxembourg	Jean-Louis Robert	Guy Berchem
Portugal	Beatriz Silva Lima	Margarida Menezes-Ferreira
Spain	Sol Ruiz	Marcos Timón
Members nominated by member states		
Austria	Bernd Jilma	Ilona G. Reischl
Belgium	Bruno Flamion	Claire Beuneu
Bulgaria	Lyubina Racheva Todorova	Rosen Georgiev
Cyprus	Anna Paphitou	Maria Vassiliou
Czech Republic	Ivana Haunerova	Alena Pychova
Denmark	Awaiting nomination	Mette Clausen
Estonia	Toivo Maimets	Awaiting nomination
Finland	Paula Salmikangas	Taina Methuen
France	Jean-Hugues Trouvin	Sophie Lucas
Germany	Egbert Flory	Martina Schüssler-Lenz
Greece	Asterios Tsiftsoglou	Vasileios Kokkas
Hungary	Balázs Sarkadi	Zsuzsanna Buzás
Iceland	Kolbeinn Gudmundsson	Awaiting nomination
Ireland	Maura O'Donovan	Niall MacAleenan
Italy	Giovanni Migliaccio	Maria Cristina Galli
Latvia	Jānis Ancāns	Aija Linē
Malta	Anthony Samuel	Awaiting nomination
Netherlands	Johannes H. Ovelgönne	Awaiting nomination
Norway	Marit Hystad	Awaiting nomination
Poland	Andrzej Mariusz Fal	Mariusz Frączek
Romania	Anca Stela Moraru	Nela Vilceanu
Slovakia	Peter Turčáni	Mikuláš Hrubiško
Slovenia	Robert Zorec	Petra Marinko
Sweden	Lennart Åkerblom	Wing Cheng
United Kingdom	Gopalan Narayanan	George Andrew Crosbie
Members representing patient organizations		
EGAN	Alastair Kent	Nick Meade
EURORDIS	Fabrizia Bignami	Michelino Lipucci di Paola
Members representing clinicians		
ESGCT	J. George Dickson	Thierry VandenDriessche
EBMT	Dietger Niederwieser	Per Ljungman

EBMT, European Group for Blood and Marrow Transplantations; EGAN, European Genetic Alliances' Network, ESGCT, European Society of Gene and Cell Therapy; EURORDIS, European Organisation for Rare Diseases.

considerations might have to be used to specifically measure toxicity, potentially at a low dose. In addition, a surgical explantation and *in vitro* propagation of cells might lead to bacterial or viral contaminations, which cannot be eliminated by sterilization. Consequently, this warrants the development of new safety methods and improved testing for potential contaminants.

One of the major clinical hurdles to overcome is the definition of the clinical target dose, as classical dose-finding strategies — that is, by selecting a dose for a confirmatory study from several tested doses in exploratory studies — may be problematic and raise the need for alternative approaches to define at least a minimally effective dose. In the field of regenerative medicine, suitable comparator treatments or products may not always be available, and a double-blind design might not be possible. Acceptable end points that were originally established for other product types may sometimes have to be adapted for a cell-based product[13]. For example, initial tumour swelling for cancer immunotherapies due to T-cell influx that would, in a common definition, represent a progression of disease owing to an increase in tumour diameter.

Certainly, such challenges are common in the development of ATMPs, and early dialogue with regulators should prove to be useful. The development concept, characterization programme and complementation by non-clinical and clinical testing are issues frequently discussed in scientific advice procedures in which the CAT is actively involved. Considering the aforementioned diversity of products and a risk-based approach, a central milestone document has already been developed by the Cell-based Products Working Party[14].

Gene therapy medicinal products

GTMPs aim at delivering a gene with the intention to obtain, through its expression, a therapeutic effect in a patient (for a legal definition see BOX 1 and REF. 2). This gene may encode a protein that is either absent or dysfunctional, or a protein that inhibits or modulates the function of a given effector structure associated with the underlying pathology. A GTMP typically functions as a sequence of different components. That is, the vector and the inserted sequence(s), the target cells modified by the vector, and finally the protein encoded by the vector and expressed upon successful gene transfer. Each of these components can contribute to either desired effects or untoward side effects[15]. This adds to the complexity of GTMPs as compared

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with other biotechnological products, and the development challenges and strategies to address them are discussed below.

Vector manufacture. Currently, the most commonly used technology for gene transfer is based on viral vectors. However, manufacturing is more challenging with viral than non-viral vectors, which can be assembled synthetically. Moreover, not all of the viral vector particles produced are biologically active, which may consequently affect vector efficacy and safety. Available manufacturing systems often yield a relatively low vector titre, which hampers clinical administration or preclinical studies in large animal models. Nevertheless, since the early recognition of these limitations in the pioneering years, significant progress has been made to ultimately overcome some of these manufacturing hurdles. For example, by improving the downstream vector processing or by alternative production systems that greatly facilitate the large-scale production of vectors[16,17]. However, adequate reference standards for testing replication-competent vectors are yet to be defined[18], and potency testing that addresses both transgene expression and its *in vivo* bioactivity needs to be performed.

Achieving stable gene expression. Treatment of inherited monogenic diseases with GTMPs typically requires stable expression of the therapeutic product. However, the duration of gene expression is influenced by various factors including the promoter used to drive the transgene, cell survival, persistence of the transgene, the immune response against the vector, the patient's cells that were genetically modified and/or the finally expressed protein, which could be recognized by the immune system as a foreign antigen[15,19].

Gene-transfer technologies have improved significantly in recent years. Consequently, it is becoming possible to overcome some of these limiting factors by choosing an appropriate type of gene delivery vector, by improving vector design or by choosing the most appropriate delivery mode for a given target tissue. The development of retargeted vectors or alternative envelopes or capsids targeting selected cell types may further improve efficacy and safety of GTMPs, and potentially even bypass humoral immune responses to the vector particles. The use of optimized cellular promoters in the appropriate target cell may also result in more sustained expression levels and reduce the risk of developing an immune response against the transgene product.

Clinical efficacy and safety. Another challenge of GTMPs relates to clinical efficacy, which is dependent on several factors, in particular the gene transfer efficiency, the ability to target the desired cell type and the expression levels of the gene of interest. These important factors vary depending on the target cell type, the type of vector used and the mode of vector administration (for example, *in vivo* or *ex vivo*, locally or systemically)[19].

A sufficient number of target cells need to be genetically modified, and the gene product needs to be expressed at a sufficient level. For example, for multifocal diseases such as myopathy it can be difficult to administer the gene locally to ensure a sufficient local distribution and expression in the affected tissue, while avoiding systemic exposure and inadvertent gene transfer into non-target cells. Safety and tolerability might be hampered by dozens of local injections per patient, and any mechanical devices used might themselves affect safety; for example, having an unwanted immune response against tissue components in case of tissue damage. Besides ethical challenges, such peculiarities of local administration also pose methodological problems for clinical trial purposes, such as blinding of the trial being difficult if not impossible. Lack of blinding can severely bias clinical results, especially when clinical read-outs are chosen that are naturally affected by knowledge of having been in the active treatment arm, for example quality-of-life read-outs.

The treatment of cancer by gene therapy is particularly challenging as it is virtually impossible to reach each cancer cell in the body. This explains why oncolytic viruses or genes that cause immune and/or cytotoxic bystander effects to enhance the therapeutic effect are currently being studied[20].

With regards to safety, insertional mutagenesis, or inadvertent alteration of gene expression that may ultimately predispose to insertional oncogenesis, is also a frequent concern. The use of strong enhancers or promoters needed to boost the efficacy of a given vector would therefore need to be weighed relative to this oncogenic risk. To minimize these risks, the vector design can be modified to prevent *cis* activation of genes that flank the integration sites and new assays have been optimized to better assess these risks[21]. Alternatively, vectors can be used that do not integrate or achieve targeted genomic integration into specific chromosomal loci[22].

Considering these various challenges and the often irreversible effects of gene transfer, the CHMP Gene Therapy Working Party has produced various scientific guidelines that help to tackle these challenges[23]. The CAT, in this tradition, will continue to expand and maintain this regulatory framework.

Combined ATMPs

Combined ATMPs are products that incorporate, as an integral part, a medical device and viable cells or tissues. Combined ATMPs are regulated under the ATMP regulations and assessed by the CAT. In addition, the medical device component must also comply with the essential requirements of the relevant medical device directive[24,25]. This aspect of conformity will usually be assessed by a suitably qualified 'notified body' for medical devices.

Potentially, a wide range of combined ATMPs will emerge as science evolves. Existing examples include tissue-engineered products incorporated onto an artificial matrix or scaffold for implantation, or living cells inserted into a special implantation device. In the future, many well-established medical devices, for example, coronary stents or pacemaker leads, may be combined with cells or tissues to improve patient outcome, making the therapeutic principles much more complex. Patient response to a combination of a medical device with cells or tissue may be different to that seen with either component alone. In addition, the performance of either component may be changed when used in combination. Thus, combined ATMPs pose challenges to finding common grounds of scientific principles on which these medicinal products are assessed to ensure quality, safety and efficacy, while meeting both the requirements of the advanced therapy and medical device regulatory frameworks. Here, interaction and collaboration between the CAT and medical device notified bodies will be valuable.

CAT involvement in development

ATMPs pose new questions and challenges to both developers and regulators. Well-established regulatory standards covering the quality, safety and efficacy criteria — set up for chemical entities and classical biologicals — need to be adapted to take into account the specificities of medicinal products that are based on genes or cells. These challenges, some of which are presented here, result in the development of alternative or additional approaches to establish the quality, safety and efficacy of ATMPs. Consequently, regulators have to be ready to enter a dialogue with developers and academic groups to exchange scientific views, while at the same time ensuring compliance with the regulatory and legal framework for the authorization of medicinal products, and more specifically for ATMPs.

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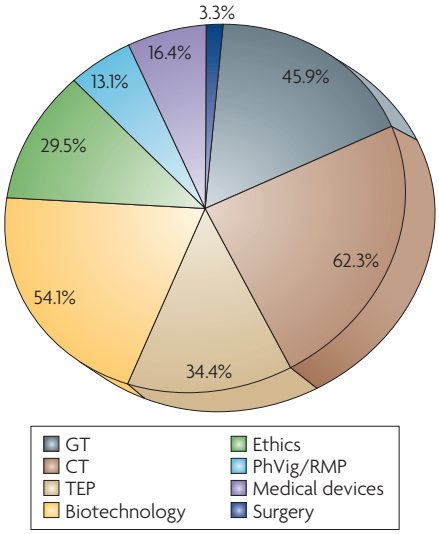

Figure 1 | **Expertise in the field of advanced therapy medicinal products declared by members and alternates of the Committee for Advanced Therapies.** Data are presented as percentage of members and alternates ($n = 61$) declaring to have expertise in the following scientific areas relevant to advanced therapy medicinal products: gene therapy (GT), cell therapy (CT), tissue-engineered products (TEP), biotechnology, ethics, pharmacovigilance and risk management planning (PhVig/RMP), medical devices or surgery. Only the expertise in the scientific areas required by the Regulation on Advanced Therapies[1] are taken up in this diagram. Note that members and alternates can have expertise in more than one of the listed scientific areas.

In Europe, the newly established CAT and the EMA Secretariat are aware of these challenges and will play an important role in early interactions. Various possibilities, already available, for interactions with companies that develop ATMPs have now been strengthened by an active involvement of the CAT. Examples are the participation of the CAT members to briefing meetings of individual manufacturers with the EMA's Innovation Task Force (ITF), and the CAT's routine involvement in all scientific advices on ATMPs. Moreover, there is the CAT's regular interactions with interested parties (that is, scientific societies, academic initiatives, patient organizations and industry associations) to discuss topics of general interest, and scientific publications by the CAT in addition to regulatory guidelines.

The ITF is a multidisciplinary group that includes scientific, regulatory and legal competences, set up to ensure EMA-wide coordination in the areas of interest and to provide a forum for early dialogue with applicants. ITF briefing meetings aim to facilitate the informal exchange of information and the provision of guidance early in the development process, and are also meant to complement and inform about existing formal regulatory procedures (such as designation of orphan medicinal products or scientific advice). As an incentive to boost the development of ATMPs, a significantly reduced fee applies to all scientific advice on ATMPs[1]. For small and medium-sized enterprises (SMEs), tailored and more extensive assistance is offered via the EMA's SME office during the product development phase and during the evaluation of the MAA.

Two new regulatory procedures, operated by the CAT in close collaboration with the EMA Secretariat and the ITF, have been set up specifically for companies developing ATMPs. These are the scientific recommendation from the CAT on the regulatory classification of the ATMP and the certification procedure, the latter being available for SMEs only.

The purpose of the classification procedure is to determine whether a given product based on genes, cells or tissues meets the scientific criteria that define ATMPs. This is in order to address, as early as possible, questions that may overlap with other areas such as cosmetics, medical devices or tissue or cell transplantation, which may arise as science develops[26].

The second new procedure, the certification procedure, is a scientific evaluation of available quality data and non-clinical data. The evaluation of early stage data by the CAT, followed by certification by the EMA, provides SMEs with a tool to enter negotiations with larger pharmaceutical companies or to attract financial support for the further development of their product, including the conduct of clinical trials. This scientific input will also assist the company in updating the quality and non-clinical parts of their dossier. The certification system therefore aims at giving the SMEs an incentive to develop ATMPs. A short procedure with ample interactions between the SME applicant, the EMA Secretariat and the CAT has therefore been developed.

Many ATMPs will be developed for rare diseases. At the EMA, the Committee for Orphan Medicinal Products (COMP) is responsible for reviewing applications seeking orphan medicinal product designation for products that diagnose, prevent or treat life-threatening or serious conditions that affect less than 5 in 10,000 persons in the European Union[27]. The CAT considers it important that there is an active and early link with the COMP for exchange of information on orphan ATMPs, which may qualify for orphan designation, and initial discussions have already commenced. Some of the CAT members were formerly members of the COMP, so there is already a clear understanding of the needs of orphan drugs in the CAT.

As regards to marketing authorization procedures for ATMPs, the CAT, with its specific expertise in the field of ATMPs, is responsible for the primary evaluation within the framework of the Centralised Marketing Authorisation procedure[28] that is mandatory for ATMPs. The review of the MAA will take no longer than 210 active days, not including the time taken by the applicant to respond to the questions posed by the CAT, or to prepare for a possible hearing in front of the CAT. During the entire process, the CAT will ensure that the CHMP, which is the EMA's main scientific committee for human medicines, is kept fully up to date of the review and discussions at the CAT. This interaction aims at facilitating the final agreement by the CHMP of the scientific opinion, prepared by the CAT, on the approval or refusal of the MAA for an ATMP. This ongoing interaction is considered by the CAT as a milestone in the top-level assessment of ATMPs, as it combines the specific expertise of the CAT for ATMPs with the long-standing expertise for other human medicines, concentrated in the CHMP. This will ensure consistency of regulatory decisions, while allowing tailoring of regulatory standards to the needs specific for ATMPs, as highlighted in this article. A procedure describing the interactions between applicants and the CAT, and between the CAT and the CHMP has been published on the EMA web site[28]. The CAT recently issued a first recommendation ('positive opinion') for approval of an ATMP to the CHMP[29]. The product is a tissue-engineered product used to repair defects in the cartilage of the knee, which is the first approval of an ATMP in Europe.

Outlook

In conclusion, the regulation on ATMPs provides a clear regulatory framework for the approval of ATMPs in the European Union. Incentives (such as fee reduction and new procedures) have been set up to assist companies developing ATMPs. From a scientific perspective, the EMA working parties have developed guidance documents specific for gene therapy and CBMPs, but owing to the broad range of products, major challenges remain for the developers of ATMPs and for the authorities reviewing the MAAs of ATMPs. The EMA is promoting an open

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dialogue with developers of ATMPs to discuss these scientific challenges, including a close interaction with the newly established specialist committee, the CAT.

The examples highlighted in this article demonstrate that the quality, safety and efficacy of ATMPs are inherently interlinked, and lack of methodologies in one discipline can often be complemented by others. Lack of a potency assay, for example, could in some cases be substituted with sound process validation and consistent manufacturing, in conjunction with clinical trial data that demonstrate that this manufacturing process leads to an efficacious product.

The three dimensions of medicinal product assessment — quality, non-clinical and clinical — are further extended for ATMPs. Often benefit–risk estimations will cross the borders to ethics; for example, a GTMP could cure an otherwise deadly disease, but cause leukaemia in some patients after many years. As the genetic disorder would be fatal and leukaemia is a potentially curable disease, the benefit–risk could still be considered positive, although sponsors and regulators would work together in an attempt to circumvent this side effect. This implies that assessment of ATMPs is a multidisciplinary exercise, requiring expertise for characterization, manufacturing and control, non-clinical, clinical and ethical aspects. All these domains are represented in the CAT.

The CAT is fully aware of and ready to meet the challenges and issues observed in ATMP development. The CAT also considers that these challenges provide opportunities for the development of novel methodologies with potentially positive effects on the development of non-ATMPs.

A full list of authors appears in Box 1.

Correspondence to Christian K. Schneider and Patrick Celis.

C.K.S. is Chairman of the CAT; Head of Division EU Cooperation/Microbiology at the Paul-Ehrlich-Institut Federal Agency for Sera and Vaccines, Paul-Ehrlich-Institut, Paul-Ehrlich-Str. 51-59, D-63225 Langen, Germany; and at the Twincore Center for Experimental and Clinical Infection Research, Feodor-Lynen-Str. 7, 30625 Hannover, Germany.

P.C. is the Scientific Secretary of the CAT and the Scientific Administrater of the European Medicines Agency, 7 Westferry Circus, Canary Wharf, London E14 4HB, UK.

e-mails: schci@pei.de; patrick.celis@emea.europa.eu

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Competing interests statement

The authors declare competing financial interests: see web version for details.

FURTHER INFORMATION

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EMEA SME Office: http://www.ema.europa.eu/SME/SMEoverview.htm
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EMEA Multidisciplinary Guidelines, including guidelines specific to ATMPs: http://www.ema.europa.eu/htms/human/humanguidelines/multidiscipline.htm
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