

Academic challenges on ATMPs' development: a regulatory perspective

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Abstract

Advanced therapy medicinal products (ATMPs) are becoming the new kid on the block for the treatment of a variety of indications with promising results. Academic centres have often been at the forefront of basic research, preclinical phases, and translational studies for the clinical development of ATMPs for several approved drugs. Despite the academic contribution to the basic and clinical research of ATMPs, undertaking a full product development process is extraordinarily challenging and demanding for academic institutions. Meeting regulatory requirements is probably the most challenging aspect for academic development, considering the limited experience and resources compared with pharmaceutical companies. The aim of this review is to present and discuss the key aspects to be considered when developing novel ATMPs from an academic perspective, based on our own experience. Emphasis is placed on understanding the regulatory requirements during the early phases of the drug development process, particularly for the preparation of a Clinical Trial Application. In general, academic centres do not possess experience in product-related documentation (such as the Investigational Medicinal Product Dossier), and therefore, early interaction with regulators is crucial to understand their requirements and receive guidance to comply with them. Tips are provided on how to manage quality, non-clinical, clinical, and risk and benefit documentation, based on our own experience and challenges. We believe this review will contribute to providing key regulatory knowledge to academic and clinical environments with the purpose of smoothing the regulatory path of ATMPs.

Academic challenges on ATMPs' development: a regulatory perspective

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Abstract (250 words)

Advanced therapy medicinal products (ATMPs) are becoming the new kid on the block for the treatment of a variety of indications with promising results. Academic centres have often been at the forefront of basic research, preclinical phases, and translational studies for the clinical development of ATMPs for several approved drugs. Despite the academic contribution to the basic and clinical research of ATMPs, undertaking a full product development process is extraordinarily challenging and demanding for academic institutions. Meeting regulatory requirements is probably the most challenging aspect for academic development, considering the limited experience and resources compared with pharmaceutical companies. The aim of this review is to present and discuss the key aspects to be considered when developing novel ATMPs from an academic perspective, based on our own experience. Emphasis is placed on understanding the regulatory requirements during the early phases of the drug development process, particularly for the preparation of a Clinical Trial Application. In general, academic centres do not possess experience in product-related documentation (such as the Investigational Medicinal Product Dossier), and therefore, early interaction with regulators is crucial to understand their requirements and receive guidance to comply with them. Tips are provided on how to manage quality, non-clinical, clinical, and risk and benefit documentation, based on our own experience and challenges. We believe this review will contribute to providing key regulatory knowledge to academic and clinical environments with the purpose of smoothing the regulatory path of ATMPs.

Introduction

Advanced therapy medicinal products (ATMPs) are those based on genes, tissues, or cells. These therapies are regulated as medicinal products for human use and are legislated under the EU Medicinal Products Directive 2009/120/EC. Accordingly, ATMPs must follow the European Medicine Agency (EMA)'s centralised procedure. However, since 2007, with the amendment of Directive 2001/83/EC and Regulation (EC) No 726/2004, member states may also establish a legal framework to allow the approval of an ATMP under very limited and restricted conditions (Hospital Exemption for academic centres).

Academic centres have been at the forefront of basic, preclinical, and clinical research for the clinical development of ATMPs for many industrial approved drugs. Indeed, during recent years, 25 ATMPs received EMA marketing authorisation, with 5 of them initially developed in academic institutions (such as the University of Pennsylvania for Kymriah® or the University of Modena and Reggio Emilia for Holoclar®). As far as we know, about 20% of currently approved ATMPs originated in an academic environment in which there was a commercial agreement with a consolidated biotech or pharmaceutical company for marketing authorisation application and product commercialisation (see **Figure 1**). Academic institutions have provided (and still provide) a major contribution to the development of ATMPs.

Less common, so far, is for an academic institution to lead the entire development of an ATMP through to regulatory approval. In this regard, academic centres face many challenges during the development of novel ATMPs. These challenges start at the very initial phases, as ATMPs must follow the established regulatory standards during the whole drug development cycle. A recently published survey focused on the academic setting showed that there is a critical lack of knowledge of regulatory science and that improved skills to navigate the complex regulatory system are clearly needed. Otherwise, lack of understanding and miscommunication between academic developers and regulatory agencies can delay, or even prevent, the development of new treatments, potentially limiting the capacity of promising academic ATMPs to reach patients. However, an early interaction between academia and regulatory bodies, through their Innovation Office, can help advance product development, in an efficient manner, towards regulatory authorisation. Some valuable regulatory information can be found within the pilot scheme "Pilot III" of the Strengthening Training of Academia in Regulatory Science (STARS) project. The STARS project has already concluded but some recommendations should be put into practice as soon as possible to increase regulatory knowledge within academia.

It goes without saying that regulatory standards must remain at the same level of rigour independently of the developing body (large pharmaceutical companies, SMEs (small and medium-sized enterprises) or academia). Accordingly, thorough regulatory training within academia is a necessity.

The aim of this review is to share with the reader a number of regulatory principles and strategies to get the academic community closer to key regulatory aspects, with particular emphasis on early phases of the ATMP drug development process. This manuscript is the result of our experience of a continuous interaction with the Spanish Agency of Medicines and Medical Devices (AEMPS) and EMA related to a number of academic ATMP initiatives carried out at our centre during the last five years. The principle objective is to discuss general aspects to be considered by academia; no product-related specific issues will be discussed in this paper.

2. ATMP lifecycle

The pharmaceutical development of a medicinal product encompasses the medicinal product lifecycle from basic research to marketing authorisation (MA) and post-marketing surveillance. In **Figure 2**, a schematic representation of the ATMP lifecycle is presented, with comments on the main critical regulatory steps required for the product development.

The development of an ATMP starts with basic research and non-clinical investigation that progresses an initial idea through to pre-clinical studies and encompasses all of the steps required before the product is administered to humans. This is followed by the clinical development phase in which the safety and efficacy of the product are evaluated on the target population through different clinical trials. In the event that the clinical evidence shows a favourable benefit-risk assessment, the applicant can submit a Marketing Authorisation Application (MAA) to achieve regulatory acceptance. At this stage, pharmacovigilance commitments are required by regulatory agencies to guarantee the surveillance of the ATMP once it is commercialised (as stated in Regulation (EC) No 1394/2007). Furthermore, ATMP regulation (Article 3(7) of Directive 2001/83) introduces the hospital exemption (HE) legal framework which allows EU member states to permit the provision of ATMPs in the absence of MA under certain conditions, subject to legislation implemented at the national level. These products must be prepared on a non-routine basis to specific quality standards for an individual patient and used within a hospital setting within the same member state in which they are manufactured under the exclusive professional responsibility of a medical practitioner.

Academic research centres and public hospitals have a prominent role in the initial phase of the ATMP development lifecycle (**Figure 2**). With a strong knowledge of patient pathology and requirements, clinicians and other workers in the hospital environment are well placed to propose new ideas for potential ATMPs. Together with non-clinical researchers and product manufacturing experts (usually from immunological departments), the development of an initial idea into a medicinal product can be materialised with enough funding capacity and a clear knowledge of the regulatory steps to follow. Sharing these initial thoughts with the regulatory agencies can help researchers to understand the regulatory requirements and to streamline non-clinical and clinical research required to support safety and efficacy studies. Indeed, scientific, and regulatory advice increase the probability of obtaining a MA. Almost 90% of applicants who obtained scientific advice and followed the advice given by the assessors received a positive opinion when applying for MA versus 40% for those who did not request scientific advice.

Clinical Trial Application and Investigational Medicinal Product Dossier

The clinical trial application (CTA) must provide comprehensive information about the investigational medicinal product and the planned trial that regulatory authorities need to assess before the initiation of the clinical trial. In academic hospitals, there is usually broad experience in designing clinical protocols and in writing the informed consent forms needed for clinical trial development. However, when facing the specific documentation of the studied medicinal product (such as the Investigational Medicinal Product Dossier, or IMPD), expertise is rather limited. Academic centres are not usually familiarised with the product-related documentation needed by regulatory agencies. This can be explained by the fact that this documentation is highly confidential, and for traditional drugs, it is owned by the pharmaceutical industry that sponsors the clinical trial. For ATMPs, in which academic centres themselves are the drug developers, investigators are forced to learn how to prepare the investigational medicinal product documentation in order to obtain clinical trial approval.

Product-related documentation needed for a CTA includes mainly 3 large pillars of information: product manufacturing, non-clinical development, and risk & benefit assessment. These 3 key aspects are discussed in the following sections of the review and the fundamental content of each section is summarised in **Figure 3**. Potential hurdles and challenges of each part are described from a public and academic hospital point of view.

Regulatory agencies need to evaluate all the scientific data accumulated on the medicinal product that has been generated during the product development stage. Therefore, all regulatory documentation must be adapted to the existing level of knowledge and the product phase of development. Moreover, when the product is first administered to humans, no information regarding clinical data is available and the ATMP risk and benefit assessment must be done using theoretical and plausible arguments based on pre-clinical results. The existing state-of-the-art must be evaluated for the medicinal product and although data from existing similar products might be complementary, they are not fundamental. Good quality data and promising non-clinical results must be clearly demonstrated for a first-in-human administration. However, in the case that the studied ATMP is already being used in the context of another trial, it is possible to cross-refer the data submitted by another sponsor and present the updated information of the product in a simple format. This can only be done with the consent of the original sponsor/developer of the medicinal product and with agreement from the authorities to allow cross referencing. Likewise, the IMPD must be constantly updated with all the acquired product data (manufactures, non-clinical experiments, updated risk & benefit and when available, clinical data).

During the product development, clinical researchers have the opportunity to interact with regulatory agencies to discuss the sufficiency and adequacy of the quality of gathered data in a scientific advice format. Applicants can present and discuss their results in a structured manner by obtaining scientific advice and formulating questions to receive regulatory feedback. This would normally include not only a critical opinion about what has been done, but also proposals of new experiments to better cover information gaps such as toxicology studies, discussion of product specifications during the manufacturing process or guidance on clinical indications for the clinical trial design and performance, among other suggestions. For an academic applicant, this formal interaction with the regulatory agencies is done through a national scientific advice (via the Innovation Office).

Product Manufacturing

ATMP manufacturing is one of the most complex steps of the pharmaceutical development. To achieve clinical trial approval, the “Quality” section of the IMPD must include a comprehensive quality report that needs to be prepared according to the specific guidelines on the quality of biological medicinal products. **Table 1** details all sections that need to be completed, as a minimum requirement, with quality data from the product under development. Information regarding the exact quality data required in each section is also detailed (**Table 1**).

We considered several critical issues that might preclude application success. These aspects need to be addressed and considered not only when manufacturing AMTPs, but also when writing the quality report for regulatory authorities:

- **Quality certification of facilities** : ATMPs must be manufactured following Good Manufacturing Practice (GMP) to accomplish regulatory standards (GMP Commission Directive 2003/94/EC). In general, academic hospitals do not possess a “pharmaceutical quality system” as their quality system is intended to ensure the best performance of care services for patients, but not to obtain a medicinal product with predefined quality characteristics. Therefore, an entirely distinct approach is required for all aspects of manufacturing an academic ATMP. Quality controls, trained personnel, certified facilities, registration and traceability of documentation, equipment validation, among many other variables, need to accomplish GMP standards. One strategy that could facilitate the achievement of GMP-compliant procedures in an academic environment is the use of closed and automated systems to manufacture ATMPs, as it is a way to minimise steps and controls. An automated and closed

system can improve process robustness and scalability while maintaining strict adherence to GMP and regulatory guidelines. Another way to improve GMP compliance is by collecting and tracking all recorded information (e.g., room temperatures, production controls, etc.) in a digital format.

- **Cost of batch analysis** : Another key challenge of ATMP production is the high cost of manufacturing each product batch. When the ATMP is manufactured as a single product batch (e.g., autologous chimeric antigen receptor T-cell therapy (referred to as CAR-T cells)), the production cost increases substantially. High cost might become prohibitive for academia as funding capacity is limited compared to conventional pharmaceutical industries. Scientific advice received by regulatory agencies becomes critical to improve cost-effectiveness when preparing the regulatory documentation. Another strategy to reduce costs in academic environments is the use of a “pre-GMP” facility to develop the manufacturing process before transferring the optimised methods to GMP suites.
- **Limited product manufacturing capacity** : Autologous-based ATMPs (such as CAR-T or tumour infiltrating lymphocytes (referred to as TILs)) cannot be produced in a mass-scale system, and therefore, ATMP manufacturing capacity is rather limited. Having a centralised manufacturing centre for ATMP supply does not appear to be a feasible strategy in terms of academic logistics and functionality. Instead, a *point-of-care* ATMPs manufacturing concept would be much more cost-effective and would increase product availability. The *point-of-care* strategy would consist of having the ATMP manufactured at the site where a patient receives care. As such, certified hospitals would be able to produce a certain ATMP, resulting in a faster supply of manufactured products in response to clinical demand and a more optimal organisation and transportation of the cellular material. In the case of CAR-T cells, for example, centralised manufacturing of the vector encoding the CAR molecule could be distributed to different hospitals with the capacity to manufacture CAR-T cells for their own patients. In this way, with strong academic collaboration, the limited product manufacturing capacity of ATMPs would be improved and expanded. This *point-of-care* ATMP production strategy requires that manufacturing hospitals are GMP certified, and that regular comparability studies are carried out to prove the equivalence of the ATMP among centres. Recommendations for comparability studies for ATMPs are described in the ICH Q5E guidelines and in a related questions and answers document. So far, this point-of-care manufacturing strategy has not been applied, but a growing interest in the potential application of such a scheme is shown by initiatives like the proposal of a regulatory framework presented by the Medicines & Healthcare products Regulatory Agency of the United Kingdom (January 2023).
- **Large product variability** : The great variability in ATMP origin (i.e., ATMP starting material) strongly impacts manufacturing standardisation. As ATMPs are biologically complex, many intrinsic variabilities are observed among products. When preparing the quality documentation for a CTA, it is essential to obtain as much information as possible regarding the product and its starting material. Analysing all of the collected data regarding the manufactured product can help in the establishment of accurate and reasonable specifications. Product specifications must be revised periodically and adjusted to experience in manufacturing the product. Efforts to reduce external variability (i.e., qualification of analytical methods, supply of starting materials) are already needed at the initial steps of product development.
- **Understanding of quality terminology** : Another common hurdle for the development of academic ATMPs is the general lack of experience in writing quality regulatory documentation. Quality data must be presented in a structured way (see **Table 1**) to regulators. European guidelines on quality, non-clinical and clinical, requirements help to gain a general idea of what must be presented. However, we found that the *learning-by-doing* strategy is certainly the most effective one to correctly report the quality results in an IMPD. Some tips that we learned during the writing of several quality reports are: i) for certain ATMPs, the drug substance and the finished product (drug product) can be closely related or nearly identical and therefore quality data can be cross-referred to avoid repetitions; ii) planning enough samples to perform future analysis is key to determine product stability under representative conditions of its storage; iii) potency assays are critical to prove the product biological activity and biomarkers assays can be accepted if the surrogacy value is reasonably established; iv) for gene-therapy

medicinal products (for example for CAR-T cells), a full quality report is needed for each starting material and all sections of the cellular product (see **Table 1**) must be written for the vector material.

In all, the preparation of quality regulatory documentation is progressive and continuous among the product development. Regulatory standards contribute to the manufacturing of robust ATMPs that can impact therapeutic response. Indeed, quality concerns of ATMPs often influence potential efficacy or safety of that product in patients. Regulatory documentation must be constantly updated and controlled to guarantee product robustness.

Non-clinical development

The initial essential step is the design of the ATMP construct itself. This process involves high-excellence basic science, of course orientated to a detected clinical need, and is highly dependent on the capabilities of the centres and experts. Once the concept is created, the safety and proof of concept non-clinical experiments also have to be developed and performed according to regulatory standards.

Non-clinical studies aim to demonstrate the safety of a medicinal product and to provide an initial proof of concept of the product mode of action, pharmacological and toxicological effects, as well as the potential efficacy. Non-clinical assays generally include the characterisation of toxic effects in relevant cell lines and target organs, dose dependence, and relationship to exposure. These data should help to define the estimated therapeutic dose-range, and the dose steps and intervals for developing clinical trials in humans. However, due to the complexity and innovative nature of ATMPs, the non-clinical development must be adapted to a tailored approach that includes principles of risk identification and mitigation. Traditional non-clinical studies and models are not always feasible with ATMPs, and this poses new challenges to developers and regulators to identify common principles that must be tested before a first-in-human clinical trial.

From our experience in non-clinical studies, there are several critical aspects that need to be addressed when writing the regulatory documentation:

- **Tailored approach for ATMPs non-clinical models** : In general, animal testing is considered necessary when it generates data that provides significant conclusions (like the identification of potential hazards for human health based on extrapolation from animal data). On the other hand, regulators commonly considered that lack of specific safety pharmacology and genotoxicity testing was acceptable for ATMPs. Furthermore, experiments were not commonly required for reproductive toxicity if there was scientific evidence demonstrating lack of exposure to reproductive organs. Conventional carcinogenicity testing was also mainly waived, as it was not considered suitable or appropriate for ATMP risk assessment. The non-clinical testing models that are usually required during the evaluation of ATMPs predominantly include the determination of toxicity endpoints by performing specific safety studies. For CAR-T cell therapies in haemato-oncological studies for example, essential results to provide include as evaluation of *on-target/off-tumour* toxicity, biodistribution analyses and assessment of *in vivo* persistence. In addition, the inclusion of efficacy studies (such as *in vitro* and *in vivo* cytotoxicity assays, measurement of pro-inflammatory cytokines, assessment of anti-tumour activity from patient-derived samples, etc.) is strongly recommended for the preparation of ATMP non-clinical regulatory documentation.
- **Model limitations** : One of the major challenges to the non-clinical development of ATMPs is the important biological differences between test species and humans. ATMPs include human cell-based products that will inevitably be rejected in an immunocompetent animal. Therefore, the use of immunocompromised animals has commonly been regarded as the only feasible alternative. However, determining the behaviour of human cell-based products in immunocompromised animals is complicated because the activity of the exogenous cells is strongly influenced by interactions with other tissues and cells of the animal model which may or may not be functional or even present at all. In general, there is a strong preference to use allogenic or autologous cells that simulate the human situation in a homologous animal (i.e., an animal that has the same disease causes, symptoms and treatment options as would humans with the same disorder). A commonly employed animal model is the NSG

or -NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl} / SzJ- strain of inbred laboratory mice. These mice allow for the engraftment of a wide range of human-derived cells and permit sophisticated modelling of many human diseases. However, the principle of the 3Rs (replacement, reduction, and refinement) needs to be considered when selecting testing approaches to be used for regulatory testing of ATMPs.

- **General tips :** It is important to realise that just by following protocols from peer-reviewed scientific publications, especially when not conducted according to regulatory standards, may not be enough to resolve uncertainties needed for regulatory approval. Moreover, it is important to note that non-clinical developers need to fully understand the product in relation to the intended use and prospectively plan the approach for successful translation of the product to the clinic. Likewise, having an in-depth understanding and knowledge of the ATMP, developers can justify their study designs, test models and tailored approach. Being able to communicate clear scientific information about the non-clinical development to regulatory authorities is strongly recommended to receive valuable input and assessment of regulators that can complement the knowledge and planning of academic developers for the progression of their product. For non-clinical regulatory documentation, academic developers must discuss the limitation of the chosen models and the relevant information that these models provide.

Another lesson learned during different clinical trial applications with ATMPs is that a safety assessment can be complemented with a discussion of potential risks or hazards in line with the recommendations discussed in the EU guideline on risk-based approach (see section 3.3 Risk & benefit assessment). Furthermore, the use of literature data can support, at least partially, the preparation of non-clinical regulatory documentation. In particular, if clinical data from very similar or identical products used for the same indication are available, these can be used to support the CTA for an ATMP. Finally, another recommendation when performing non-clinical research is that for key studies (such as biodistribution or toxicity assays), researchers must use the product intended for clinical use (i.e., the product must be representative of the product material used in patients).

Risk & benefit assessment

Current regulatory recommendations establish that a risk-based approach involves recognising the potential risks linked to the clinical application of an ATMP and the inherent risk factors of the ATMP itself in terms of quality, safety and efficacy. A risk-based approach helps to anticipate potential risks associated with a new product, and judge if they are acceptable when balanced with the potential benefit. Therefore, the risk-benefit assessment of the investigational medicinal product must be included in the regulatory documentation with an overall assessment and measurement of favourable and unfavourable effects. This assessment can be quantitative (i.e., adverse events incidence or prevalence in a clinical trial) or qualitative (i.e., description of relevant data from literature and associated risk factors), depending on the therapeutic context and clinical study design, but must clearly discuss the expected clinical relevance of the benefits, the importance of risks (both identified and potential risks) and the impact of uncertainties and limitations of that analysis.

From our experience in the assessment of the risk-benefit balance of academic-developed ATMPs, we consider the following barriers:

- **Risk characterisation:** Because ATMPs predominantly cover an unmet medical need, the potential benefit is usually easier to characterise than the possible risks. However, when it comes to risk evaluation, the lack of previous experience makes this particular hurdle even larger. As explained above for non-clinical development, conventional safety testing is not always available for ATMPs and there are model limitations. Moreover, relevant literature is scarce, and mostly pertains to early development phases, with little information in humans. Therefore, the risk assessment in the pre-clinical phase is in many cases based on the early detection of safety signals, and in most instances, is difficult to translate into humans. In any case, the applicant is obliged to describe in a tabular form: i) hypothetical risks (based on literature review and elucidation of its mechanism of action), ii) a corresponding description and/or discussion, iii) known and potential features that may have an impact (protective or risk factors) on patient safety, and iv) risk minimisation strategies to be implemented. Even though this information remains mostly descriptive and qualitative, displaying the data in this way allows for better

categorisation of the risks and provides a clearer presentation and understanding of the data. Adequate and sensible planning of risk mitigation strategies is a necessary exercise to reduce uncertainties, thus helping the risk-benefit balance lean towards the positive side.

- **Risk Heterogenicity:** ATMPs are complex products that differ in clinical development and manufacturing process for each product, even when they are used for the same indication. Therefore, risks will also differ for each ATMP. To describe the risks associated with a specific ATMP, it is important to have a comprehensive background in every step of the development of the medicinal product. This means thorough understanding of not only the target and mechanism of action, but also of the manufacturing process, ATMP structure, route of administration, indication and pre-clinical development. As an example, some CAR-T cell products with a CD28 co-stimulatory domain have been linked to early development of cytokine release syndrome in comparison to CAR-T cells designed with 4-1BB .
- **Other regulatory tools and documentation**

To complete the CTA (see **Figure 2**), other information related to the clinical trial related information is also required. These documents are evaluated by regulatory agencies (through the Clinical Trials Information System (CTIS)) and by local ethical committees. Clinical trials must follow Good Clinical Practice guidelines (influenced by the Nuremberg Code) to guarantee that the investigational drug administration to humans has the lowest health risk to patients in the tested conditions. The most relevant information presented to health regulatory authorities is the clinical protocol which details the exact steps to be taken to test the new medication on humans. The key aspects that need to be included in the clinical protocol are the study population, the dose selection and the safety monitoring plan. Other relevant documentation includes the patient informed consent form, that must be clear and comprehensible for patients and the investigator's brochure (IB), that summarises all the known non-clinical and clinical safety and efficacy data of the medicinal product. All these documents must be prepared and updated for each clinical trial, and they must contemplate the necessary precaution to protect the safety of the clinical study subject.

General discussion

Advanced therapies have been a reality as a therapeutic tool for several years now. Europe has already approved 25 ATMPs. The potential for developing advanced therapies is virtually limitless, offering the possibility of developing new, relatively personalised therapeutic strategies for multiple unmet medical conditions.

From the beginning, the collaboration between academic centres (drug discovery) and the pharmaceutical industry (drug development and marketing authorisation) has been a common practice in this field. Academic centres play a fundamental role in identifying unmet medical needs, therapeutic targets, and the development of the basic science underlying the entire medical process. However, in recent years, some academic centres have completed the entire process of developing advanced therapies that have become available to patients in some European countries. Specifically, in Spain, there are two products in this category (NC1 and ARI-0001). These milestones have been made possible thanks to the legislative development of the so-called "hospital exemption", a provision available throughout the EU and implemented in the majority of countries, but with different regulatory requirements among member states.

Hospital exemption is only possible to obtain national authorisation with very limited indications (mainly unmet medical needs) and limited access conditions (restricted to a hospital centre or a few centres). Therefore, under current conditions, it is difficult to envision this regulatory pathway as a real solution for accessing these medicines within the EU. Harmonised legislative development among EU member states would be necessary to ensure that this access occurs uniformly throughout Europe. Only coordinated political will is likely to lead to future solutions within this regulatory framework.

In this regard, the initiative of the EMA to provide the necessary regulatory tools to academia for facilitating global access in the EU is appreciated. With this initiative, academic centres can be offered the possibility of obtaining a centralised authorisation for the entire EU.

Unfortunately, the existence of different access pathways does not eliminate all barriers to the development of ATMPs. The complete development of advanced therapies, while adhering to current regulatory requirements,

remains a challenge for academic centres. There are multiple reasons that could explain these difficulties:

1. **Regulatory knowledge:** Regulatory expertise is not abundant in academia. Despite its slow growth, there are a few centres that have experts in drug regulation who understand the philosophy and underlying science of regulatory principles, recognize the importance of drug regulation in protecting citizens, and can use the terminology required by the regulator. Therefore, it is critical for academic centres intending to develop new medicines to acquire the necessary expertise. Probably due to lack of awareness, there seems to be a certain mutual distrust between regulatory agencies and academia. Academics tend to think that regulations establish unnecessary barriers that hinder patient access to promising therapies. Regulators, on the other hand, doubt whether academic applicants are aware of the importance of protecting patient safety and complying with basic regulatory requirements (such as GMP, GLP (good laboratory practice), and GCP (good clinical practice)). These barriers can only be overcome through continuous dialogue between both parties. Indeed, regulatory agencies have official platforms (such as the Innovation Office of AEMPS (*innov_spain@aemps.es*)) that facilitate and promote an early interaction between researchers and regulators. And recently, the EMA has launched a pilot study to support academic and non-profit institutions to develop ATMPs. It is crucial for researchers to become aware of the importance of weighing risks and designing a risk minimisation plan that progressively advances basic research to the clinic. Additionally, some regulators should understand that a risk minimisation strategy should not turn into risk avoidance, as this leads to the stagnation of development.
2. **Capacity to meet production demands:** It is not difficult to imagine that for ultra-rare diseases with very low prevalence, producing a medicine for the entire Europe, even in a single academic centre, may be an achievable goal. However, for more prevalent indications (even if they are rare diseases), ensuring that manufacturing can meet actual needs is a tremendous challenge. The pharmaceutical industry has the means to establish production centres on a global scale, something that is not possible for academia. One way to alleviate this difficulty in certain types of advanced therapies (such as CAR-T cells) could be the implementation of the Point of Care model. According to this model, lentiviral production is carried out by the developing centre, while cell production takes place at the centre where the medicine is administered. This model offers significant advantages in terms of accessibility, patient convenience, and production speed. However, it is not without complications, as the regulatory requirements of educating, establishing, accrediting, inspecting, and maintaining cell production with demonstrated comparability in multiple centres requires significant financial and regulatory efforts to ensure consistent and quality production in all manufacturing centres.
3. **Maintenance of marketing authorisation throughout the product lifecycle:** There is no doubt that early patient access to these therapies is the main objective of any academic or industrial initiative, but it is not the only or final objective. It is essential to maintain the use of the medicine under optimal safety and efficacy conditions, ensure manufacturing adheres to the strictest quality principles, and to be responsible for the product throughout its lifespan by periodically updating safety and efficacy data and reporting them to the competent authority. This requires a long-term vision and necessary resources that academia must progressively acquire.

In conclusion, the authors believe that we are at the beginning of a path that is yet to be fully defined. The increasing attention that regulatory authorities are paying to academic initiatives in this field (such as the Innovation Office of the AEMPS and the Academic Initiative of the EMA) is common knowledge. We believe that these are suitable and necessary instruments for involving and engaging academia in the development of ATMPs while meeting all quality, safety, and efficacy requirements. This commitment should be mutual, with academia deepening its understanding of applicable regulatory requirements.

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Conflicts of interest

The views expressed in this article are those of the authors and do not necessarily represent the views or policies of the Spanish Agency of Medicines and Medical Devices (AEMPS) or the Hospital Clinic de Barcelona (HCB). All authors declare that they have no competing interests.

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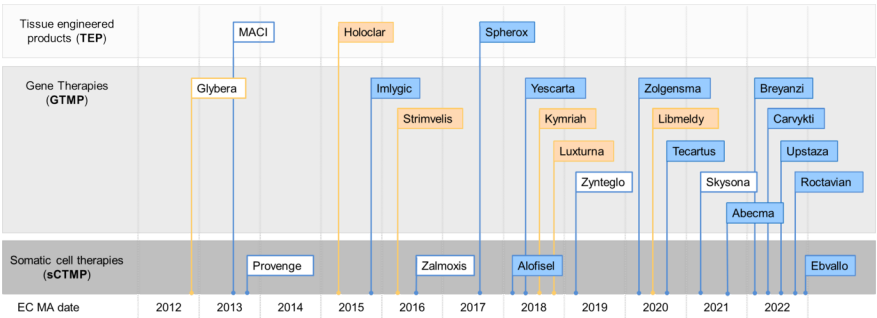


Figure 1 . Approved ATMPs in the EU from 2012 to 2022. Blue boxes show ATMPs for which the sponsor is either a pharmaceutical company or a private biotech while orange boxes are those that originally come from an academic centre (universities and hospitals) but developed and commercialised by a pharmaceutical company. For example, Kymriah[®], was originally developed at the University of Pennsylvania and bought by Novartis who performed all the pharmaceutical development and commercialisation. Filled boxes are ATMPs that are currently authorised by the EMA while empty boxes show withdrawn products. This figure is adapted from the CAT quarterly highlights and approved ATMPs document.

Figure 2. Overview of the lifecycle of an ATMP (key steps of the drug pharmaceutical development). Adapted from the slides of the STARS Pilot III Regulatory Support project. Figure prepared with Biorender[®].

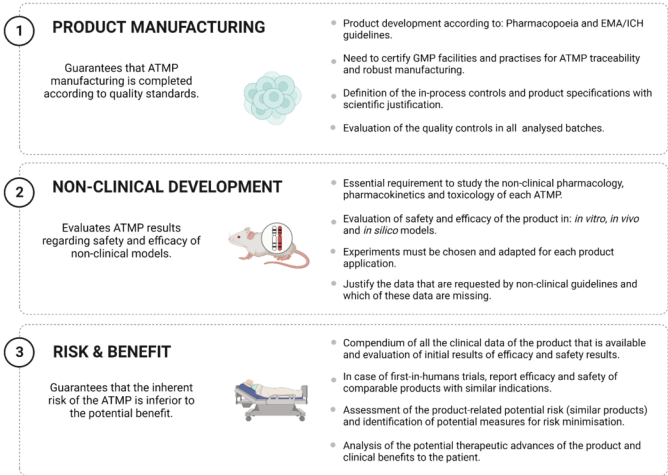


Figure 3. Schematic summary of the main product-related regulatory content needed for a clinical trial application. Figure prepared with Biorender®.

IMPD/ CTD section	Requirements applicable to all ATMPs
3.2.S. Drug Substance	3.2.S. Drug Substance
3.2.S.1. General information	· Nomenclature of the product. · Information on the structural component and summary of the physical and biological characteristics of the substance. · General physicochemical properties of the active substance.
3.2.S.2. Manufacture	· List of manufacturers of the active substance. · Summary of the manufacturing process (complete flowchart and reagents used should be included). · Controls of materials (e.g., raw materials, starting materials, reagents) · Controls of critical steps and intermediates of the active substance. · Description of any development work done to optimise the production operations.
3.2.S.3. Characterization	· Elucidation of structure and other characteristics. · Impurities (process-related impurities and cellular impurities).
3.2.S.4. Control of the drug substance	· Specifications (for the active substance release). · Description of the analytical methods used for testing the active substance. · Suitability, qualification, or validation data of the analytical methods used (depend on the status of the product development). · Batch analysis (tables of all the manufactured data of the active substance). · Justification of specifications.
3.2.S.5. Reference Standards or Materials	· Characterization of the batch substance to establish a reference standard (only in case of international standards available).
3.2.S.6. Container Closure System	· Information on the immediate packing material.
3.2.S.7. Stability	· Data of storage conditions (in case it is not immediately processed).
3.2.P. Drug Product	3.2.P. Drug Product
3.2.P.1. Description and composition	· Qualitative and quantitative composition of the finished medicinal product.
3.2.P.2. Pharmaceutical development	· Short description of the formulation development and justification of using any new pharmaceutical form or excipient.
3.2.P.3. Manufacture	· List of manufacturers of the drug product. · Description of the manufacturing process and controls. · Control of all material used in the manufacture of the substance. · Control of critical steps and intermediates. · Process validation and/or evaluation. · Manufacturing process development.
3.2.P.4. Control of excipients	· References to the pharmacopoeia for the excipient's specifications.

IMPD/ CTD section	Requirements applicable to all ATMPs
3.2.P.5. Control of the medicinal product	· Drug product specifications (quality attribute) for product release. · Analytical procedures and validation of these analytical methods. · Batch analysis (with data from all the manufactured drug products). · Additional impurities observed in the medicinal product. · Justification of the specifications (for product release).
3.2.P.6. Reference Standards or Materials	· Parameters for characterisation of reference standards (where applicable).
3.2.P.7. Container Closure System	· Information on the immediate packaging material.
3.2.P.8. Stability	· Stability studies of the medicinal product.

Table 1. Summary of the main regulatory requirements for the quality documentation. Table adapted from the *Guideline on the minimum quality and non-clinical data for certification of ATMPs* .