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. 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. This review aims to outline the key aspects to be considered when developing novel ATMPs from an academic perspective, based on the results of our own experience and interaction with the Spanish Agency of Medicines and Medical Devices (AEMPS) and European Medicine Agency (EMA) related to a number of academic ATMP initiatives carried out at our centre during the last five years. 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. Academic centres usually lack expertise 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. Insights are shared on managing quality, non-clinical, clinical, and risk and benefit documentation, based on our own experience and challenges. This review aims to empower academic and clinical settings by providing crucial regulatory knowledge to smooth the regulatory journey of ATMPs.

1. Introduction

Advanced therapy medicinal products (ATMPs) are those based on genes, tissues, or cells[1,2]. These therapies are regulated as medicinal products for human use and are legislated under the EU Medicinal Products Directive 2009/120/EC[3]. 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)[4,5].

Academic centres have been at the forefront of basic, preclinical, and clinical research for the clinical development of ATMPs for many industrial approved drugs[6]. Indeed, during recent years, 24 ATMPs received EMA marketing authorisation, with 6 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®)[7,8].About 25% 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[9].

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[10] . 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[11]. 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[12]. Some valuable regulatory information can be found within the pilot scheme "Pilot III" of the Strengthening Training of Academia in Regulatory Science (STARS) project, which emerged from the collaboration between European National Competent Authorities (NCAs), the EMA and associated countries[12]. The STARS project has already concluded but some recommendations should be put into practice as soon as possible to increase regulatory knowledge within academia[13].

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 principal 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 lifecycle of an ATMP follows a quality-by-design (QbD) approach centred in a risk-management methodology that is adapted to the specific development phase. This lifecycle starts with basic research and non-clinical investigation that progresses an initial idea through pre-clinical studies and encompasses all the steps required before the product is administered to humans with a special focus on quality specifications and preclinical regulatory requirements. This is followed by the clinical development phase in which safety and dose finding is explored in early-phase clinical trials, and relevant clinical endpoints are assessed in confirmatory pivotal clinical trials. Risk-benefit is continuously assessed and updated throughout the whole product lifecycle development. In the event that the clinical evidence shows a favourable benefit-risk assessment after clinical safety and efficacy data have been obtained in confirmatory studies, the applicant can submit a Marketing Authorisation Application (MAA) to achieve regulatory acceptance. At this stage, specific 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[14]). Risk-benefit should be updated thereafter periodically with post-authorization data.

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 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 from the EMA[15].

3. 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[16,17]. **Table 1** aims to summarize all the required documents to be presented in the European Union and European Economic Area via the Clinical Trial Information System (CTIS) for CTA. These listed documents are classified according to the CTIS section and include a brief description of the information to be covered, together with the organism responsible for its assessment (national competent authorities, ethics committees of the EU member state, or both).

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.

Regarding trial-related documentation, one important document is the clinical protocol which details the exact steps to be taken to test the new medication on humans[16]. 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 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 (see **Table 1** for further details).

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 (manufacturers, 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[18,19]. 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. These regulatory support interactions for academic applicants might be stablished at national level (e.g. via the Innovation Office at the AEMPs, Spain)[18] or at European level (via the Scientific Advice portal)[20].

3.1. 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[21]. **Table 2** 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 2**).

We considered several critical issues that might preclude application success. These aspects need to be addressed and considered not only when manufacturing ATMPs, 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[22] (GMP Commission Directive 2003/94/EC[23]). 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[24]. 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[24]. 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[25]. An automated and closed system can improve process robustness and scalability while maintaining strict adherence to GMP and regulatory guidelines[26]. 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[8]. 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[26].

- **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[26].To retain a centralized manufacturing does not appear feasible due to cost for academic facilities and limited capacity to supply and fulfil both, infrastructure requirements and patient supply demands beyond the producing hospital[27,28]. Instead, decentralized manufacturing, also referred as a *point-of-care* ATMPs manufacturing

concept, would be much more cost-effective and would increase product availability[29]. 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[30–32]. 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. Of note, significant regulatory hurdles are raised for the ATMPs owner when multi-centre production is used for the same drug product. The *point-of-care* ATMP production must comply with regulatory requirements such as GMP certification for manufacturing hospitals or regular comparability studies to prove the equivalence of the ATMP among centres. Recommendations for comparability studies for ATMPs are described in the ICH Q5E guidelines[33] and in a related questions and answers document[34] 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)[32].

- **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 appropriate 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.

- **Identification of critical quality attributes**: Understanding the parameters that will affect the quality of the product is key for a quality by design approach in the development of ATMPs[35]. This approach enables an optimized manufacturing of the product, implementing an analytical and risk-management methodological approach in the design, development, and manufacturing of ATMPs. The identification of critical and non-critical parameters of the product manufacturing process is essential to maximize the production capacity and reduce unappropriated tests that might increase cost and production time (see recommendations on the ICH Guideline Q8 (R2) on Pharmaceutical Development[36].

- **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 understand 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[38]; ii) planning enough samples to perform future analysis is key to determine product stability under representative conditions of its storage[18]; iii) potency assays are critical to prove the product biological activity and biomarkers assays can be accepted if the surrogacy value is reasonably established[39,40]; 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.

3.2. 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[41]. 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[41]. 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[42]. 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)[42]. 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[42]. Conventional carcinogenicity testing was also mainly waived, as it was not considered suitable or appropriate for ATMP risk assessment[42]. 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 the haemato-oncological field, essential results considered to provide include the evaluation of *on-target/off-tumour* toxicity, biodistribution analyses and assessment of *in vivo* persistence[43]. 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[42]. 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[42]. 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[44]. 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[45].

- **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)[42,46]. 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).

3.3. 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[46]. 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[47].

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[46]. 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 Heterogeneity:** 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 [48].

3.4. Other regulatory tools and documentation

To complete the CTA (see **Figure 2**), other information related to the clinical trial related information is also required, such as the requirements on data protection collected in accordance with Regulation (UE) 2016/679 and the applicable rules for collection, storage, and future use of biological samples from the clinical trial. Another relevant document is the authorization of the voluntary release of genetic modified organisms (GMOs) certificate. To date, this document is country-dependent which means that it is

provided in each member state according to their national requirements. As an example, in the case of Spain, this GMO certificate is granted from the Ministry for the Ecological Transition and the Demographic (MITECO).

These documents, together with the mentioned in **Table 1**, are evaluated by regulatory agencies (through the Clinical Trials Information System (CTIS)[49]) 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.

4. 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[50–52]). 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 restricted to national use of the ATMP and only for 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 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[53]. 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.

Bibliography

1. EMA. Advanced Therapies Medicinal Products: Overview. *https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview* (2022).

2. European Comission. Advanced Therapies. https://ec.europa.eu/health/medicinal-products/advanced-therapies_es (2022).

3. Official Journal of the European Union. *Comission Directive 2009/120/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products*. (2009).

4. Hills, A. *et al.* An assessment of the hospital exemption landscape across European Member States: regulatory frameworks, use and impact. *Cytotherapy* **22**, 772-779.e1 (2020).

5. Cuende, N. *et al.* Patient access to and ethical considerations of the application of the European Union hospital exemption rule for advanced therapy medicinal products. *Cytotherapy* **24**, 686–690 (2022).

6. Hildebrandt, M. Horses for courses: an approach to the qualification of clinical trial sites and investigators in ATMPs. *Drug Discovery Today* vol. 25 265–268 Preprint at https://doi.org/10.1016/j.drudis.2019.10.003 (2020).

7. de Wilde, S. *et al.* Development of cell therapy medicinal products by academic institutes. *Drug Discovery Today* vol. 21 1206–1212 Preprint at https://doi.org/10.1016/j.drudis.2016.04.016 (2016).

8. Pearce, K. F. *et al.* Regulation of advanced therapy medicinal products in Europe and the role of academia. *Cytotherapy* **16**, 289–297 (2014).

9. Urbano-Ispizua, A. & Hudecek, M. CART Initiatives in Europe. in *The EBMT/EHA CAR-T Cell Handbook* 23–28 (2022).

10. Salmikangas, P. Challenges during the development of ATMPs. https://www.ema.europa.eu/en/documents/presentation/presentation-challenges-during-development-advanced-therapy-medicinal-products-paula-salmikangas_en.pdf (2014).

11. Kallio, M. J. *et al.* Translating academic drug discovery into clinical development: a survey of the awareness of regulatory support and requirements among stakeholders in Europe. *Clin Pharmacol Ther* (2022) doi:10.1002/cpt.2789.

12. STARS consortium. Strengthening Training of Academia in Regulatory Science. *https://www.csa-stars.eu/* (2021).

13. Starokozhko, V. *et al.* Strategic recommendations from the STARS project to foster academic drug development. *Nature Reviews Drug Discovery* Preprint at https://doi.org/10.1038/d41573-023-00021-z (2023).

14. Official Journal of the European Union. Regulation (EC) Nº 1394/2007 of the european parliament and of the council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) Nº 726/2004. *13 November 2007* vol. 324 122 Preprint at http://care.diabetesjournals.org/content/28/9/2155.abstract%0Ahttps://doi.org/10.1007/BF02968135 (2007).

15. Hofer, M. P. *et al.* Regulatory watch: Impact of scientific advice from the European Medicines Agency. *Nat Rev Drug Discov* **14**, 302–303 (2015).

16. Chiodin, D., Cox, E. M., Edmund, A. v., Kratz, E. & Lockwood, S. H. Regulatory Affairs 101: Introduction to Investigational New Drug Applications and Clinical Trial Applications. *Clin Transl Sci* **12**, 334–342 (2019).

17. European Commission website. EudraLex - Volume 10 - Clinical trials guidelines. *https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en* (2023).

18. AEMPS. Pilot III: Regulatory Support to Spanish Academia from STARS Core to Comprehensive Curriculum. https://www.csa-stars.eu/Pilot-III-Implementing-the-Comprehensive-Curriculum-1761.html (2022).

19. Spanish Agency of Medicines and Medical Devices. Office for support of Innovation and knowledge of medicinal products. *https://www.aemps.gob.es/medicamentos-de-uso-humano/oficina-de-apoyo-a-la-innovacion-y-conocimiento-sobre-medicamentos/?lang=en*.

20. European Medicines Agency Guidance for Companies requesting Scientific Advice and Protocol Assistance. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-guidance-applicants-seeking-scientific-advice-protocol-assistance_en-0.pdf.

21. European Medicines Agency. *EMA/CAT/80183/2014 Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products*. www.ema.europa.eu/contact (2018).

22. European Comission EudraLex. Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products. https://health.ec.europa.eu/system/files/2017-04/pharm731_2ib_atmps_guidelines_0.pdf (2017).

23. Commission Directive. 2003/94/EC Laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. *Official Journal of the European Union* (2003).

24. Viganò, M., Giordano, R. & Lazzari, L. Challenges of running a GMP facility for regenerative medicine in a public hospital. *Regenerative Medicine* vol. 12 803–813 Preprint at https://doi.org/10.2217/rme-2017-0051 (2017).

25. Kropp, M. *et al.* GMP-Grade Manufacturing and Quality Control of a Non-Virally Engineered Advanced Therapy Medicinal Product for Personalized Treatment of Age-Related Macular Degeneration. *Biomedicines* **10**, 2777 (2022).

26. Silva, D. N. *et al.* ATMP development and pre-GMP environment in academia: a safety net for early cell and gene therapy development and manufacturing. *Immuno-Oncology and Technology* **16**, 100099 (2022).

27. Harrison, R. P., Rafiq, Q. A. & Medcalf, N. Centralised versus decentralised manufacturing and the delivery of healthcare products: A United Kingdom exemplar. *Cytotherapy* **20**, 873–890 (2018).

28. Medcalf, N. Centralized or decentralized manufacturing? Key business model considerations for cell therapies. *Cell Gene Ther Insights* **2**, 95–109 (2016).

29. Wilson, A. & Cockroft, A. Regulatory considerations for decentralized manufacture of ATMPs. *Cell Gene Ther Insights* **5**, 1213–1224 (2019).

30. Lancu, E. M. & Kandalaft, L. E. Challenges and advantages of cell therapy manufacturing under Good Manufacturing Practices within the hospital setting. *Current Opinion in Biotechnology* vol. 65 233–241 Preprint at https://doi.org/10.1016/j.copbio.2020.05.005 (2020).

31. Priesner, C. & Hildebrandt, M. Advanced Therapy Medicinal Products and the Changing Role of Academia. *Transfusion Medicine and Hemotherapy* vol. 49 158–162 Preprint at https://doi.org/10.1159/000524392 (2022).

32. Medicines & Healthcare products Regulatory Agency. Consultation on Point of Care manufacturing. *https://www.gov.uk/government/consultations/point-of-care-consultation/consultation-on-point-of-care-manufacturing* (2023).

33. European Medicines Agency. *CPMP/ICH/5721/03 - ICH Topic Q 5 E Comparability of Biotechnological/Biological Products*. http://www.emea.eu.int (2005).

34. *EMA/CAT/499821/2019 Comparability considerations for Advanced Therapy Medicinal Products (ATMP) - Questions and answers*. (2019).

35. European Medicines Agency. Quality by design | European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/research-development/quality-design (2021).

36. European Medicines Agency. EMA/CHMP/ICH/167068/2004 - ICH Topic Q8 (R2) Pharmaceutical Development. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002872.pdf.

37. European Medicines Agency. *EMA/CAT/852602/2018 Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials*. www.ema.europa.eu/contact (2019).

38. Cat. *EMA/CAT/486831/2008/corr Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products*. www.ema.europa.eu (2010).

39. European Medicines Agency. EMA/CPMP/ICH/2887/1999 ICH guideline M4 (R4) on common technical document (CTD) for the registration of pharmaceuticals for human use-organisation of CTD. vol. 4 Preprint at www.ema.europa.eu/contact (2021).

40. European Medicines Agency. *EMA/CHMP/BWP/271475/2006 rev.1 Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer*. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-potency-testing-cell-based-immunotherapy-medicinal-products-treatment-cancer-revision-1_en.pdf (2016).

41. Caballero-Garrido, E., Martin Blanco, N. & Gracia Moneva, B. A preclinical regulatory approach before clinical development and marketing authorization of medical products in the European Union. *Am J Drug Deliv* **07**, 2321 (2019).

42. Vestergaard, H. T., Apote, L. D., Schneider, C. K. & Herberts, C. The evolution of nonclinical regulatory science: Advanced therapy medicinal products as a paradigm. *Molecular Therapy* vol. 21 1644–1648 Preprint at https://doi.org/10.1038/mt.2013.175 (2013).

43. Hartmann, J., Schüßler-Lenz, M., Bondanza, A. & Buchholz, C. J. Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts. *EMBO Mol Med* **9**, 1183–1197 (2017).

44. Ito, M. *et al.* NOD/SCID/γcnull mouse: An excellent recipient mouse model for engraftment of human cells. *Blood* **100**, 3175–3182 (2002).

45. EMA/CHMP/CVMP/JEG-3Rs/450091/2012 Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches. 1–12 (2016).

46. European Medicine Agency. EMA/CAT/CPWP/686637/2011 Guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products. 1–18 Preprint at (2013).

47. Dunder, K. *Benefit-risk assessment for initial marketing authorisations and standard of evidence*. https://www.ema.europa.eu/en/documents/presentation/presentation-module-7-benefit-risk-assessment-good-regulatory-practice_en.pdf (2018).

48. Neelapu, S. S. *et al.* Chimeric antigen receptor T-cell therapy-assessment and management of toxicities. *Nature Reviews Clinical Oncology* vol. 15 47–62 Preprint at https://doi.org/10.1038/nrclinonc.2017.148 (2018).

49. European Medicines Agency. *EMA/299895/2021 Clinical Trials Information System (CTIS)-Sponsor Handbook*. https://www.ema.europa.eu/en/documents/other/clinical-trial-information-system-ctis-sponsor-handbook_en.pdf (2021).

50. Trias, E., Juan, M., Calvo, G. & Urbano-Ispizua, Á. The hospital exemption pathway for the approval of advanced therapy medicinal products: an underused opportunity? The case of the CAR-T ARI-0001. *Bone Marrow Transplant* **57**, 156–159 (2022).

51. Ortíz-Maldonado, V. *et al.* CART19-BE-01: A Multicenter Trial of ARI-0001 Cell Therapy in Patients with CD19+ Relapsed/Refractory Malignancies. *Molecular Therapy* **29**, 636–644 (2021).

52. Spanish Agency of Medicines and Medical Devices (AEMPS). Autorizaciones de uso de medicamentos de terapia avanzada. *https://www.aemps.gob.es/medicamentos-de-uso-humano/terapias-avanzadas/autorizaciones-de-uso-de-medicamentos-de-terapia-avanzada/?lang=en*.

53. European Medicines Agency. EMA pilot offers enhanced support to academic and non-profit developers of advanced therapy medicinal products. *https://www.ema.europa.eu/en/news/ema-pilot-offers-enhanced-support-academic-non-profit-developers-advanced-therapy-medicinal-products* (2022).

54. European Medicines Agency. *EMA/CAT/841175/2022 - CAT quarterly highlights and approved ATMPs*. https://www.ema.europa.eu/en/documents/report/cat-quarterly-highlights-approved-atmps-october-2022_en.pdf (2022).

55. European Parliament and Council of the European Union. *Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC*. *Official Journal of the European Union* (2014).

56. European Medicines Agency. EMA/299895/2021 Clinical Trials Information System (CTIS)-Sponsor Handbook. https://www.ema.europa.eu/en/documents/other/clinical-trial-information-system-ctis-sponsor-handbook_en.pdf (2021).

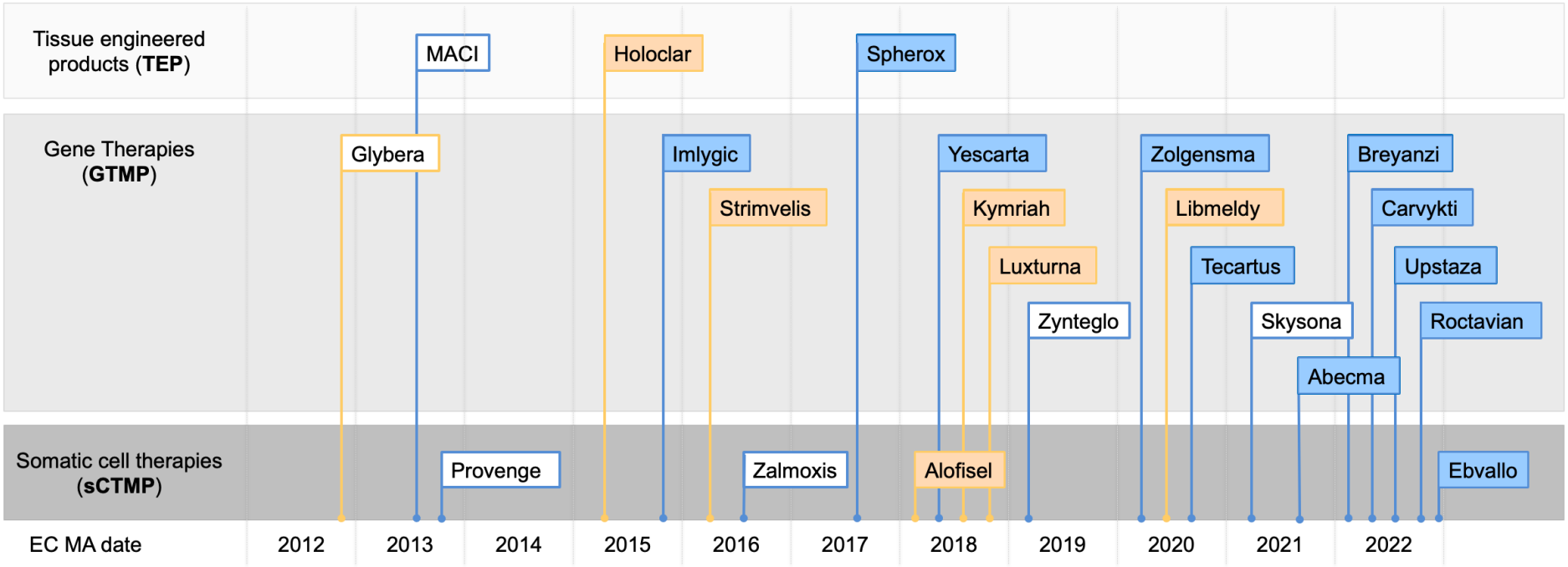

Figure 1. Approved ATMPs in the EU from 2012 to 2022. Blue boxes show ATMPs for which the sponsor is either a pharmaceutical company or a private biotech while orange boxes are those that originally come from an academic centre (universities and hospitals) but developed and commercialised by a pharmaceutical 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[54].

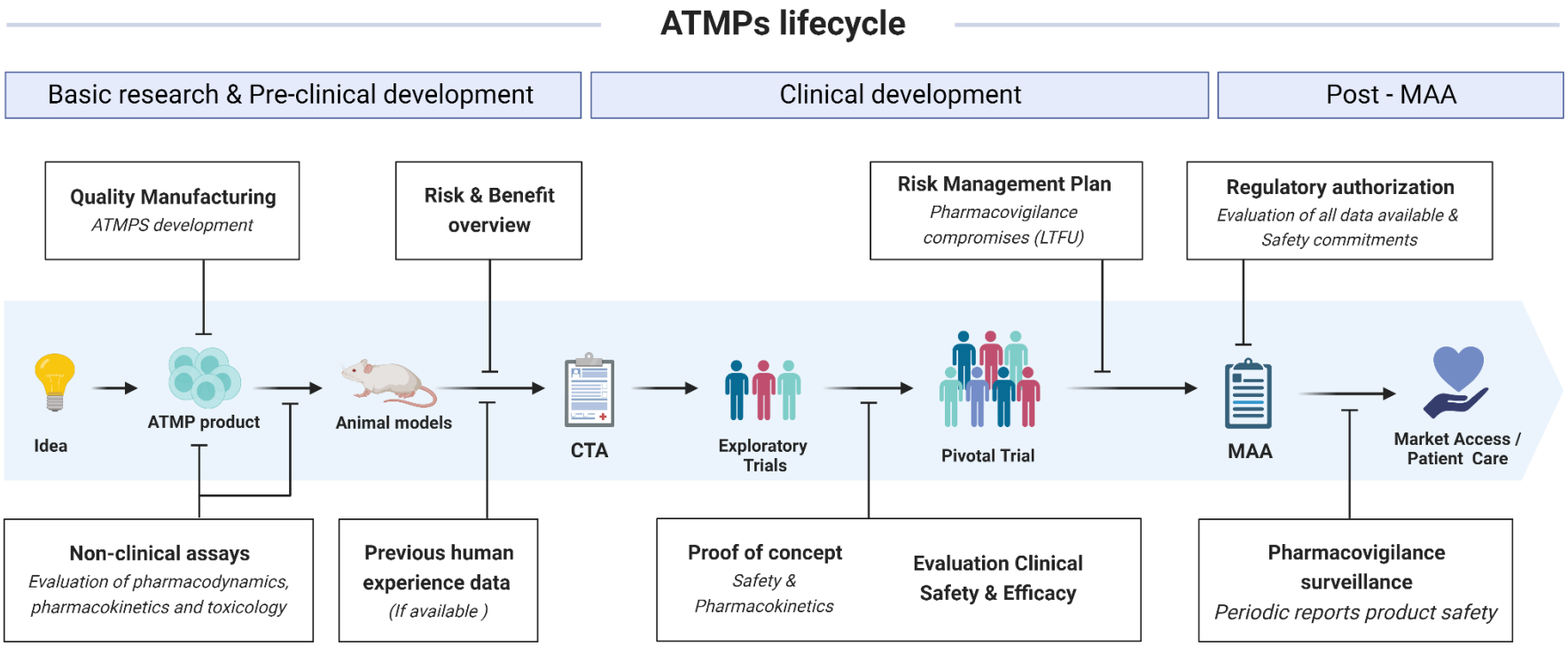

Figure 2. Overview of the lifecycle of an ATMP (key steps of the drug pharmaceutical development). Adapted from the slides of the STARS Pilot III Regulatory Support project[18]. Figure prepared with Biorender®.

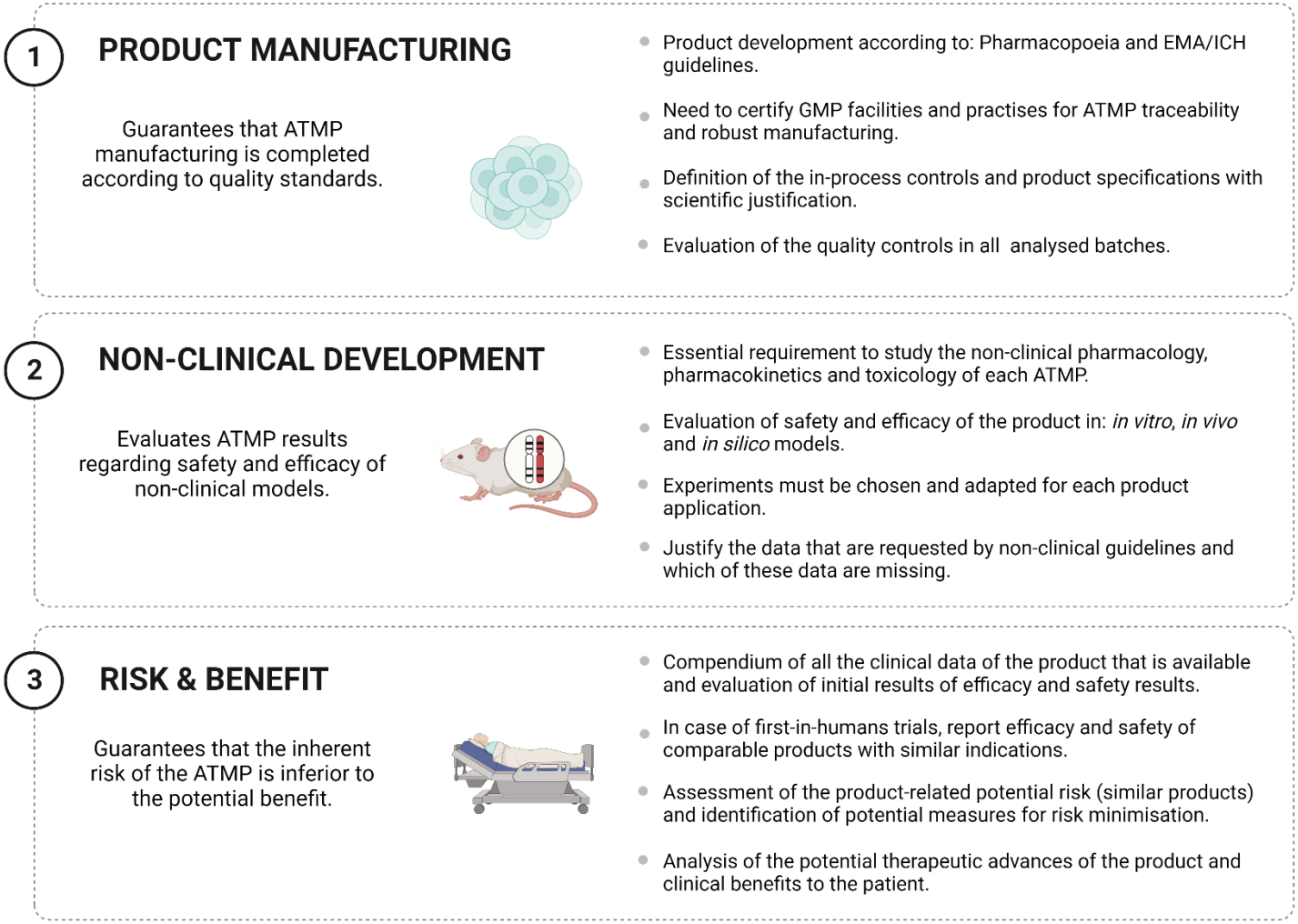

Figure 3. Schematic summary of the main product-related regulatory content needed for a clinical trial application. Figure prepared with Biorender®.

CTA subsections	Brief description / List of documents required
Form section	
Initial Application Details	
Cover letter	The cover letter contains essential information about the clinical trial, such as the EU trial number, product name, sponsor name, and highlights any specific features particular to the clinical trial. It is not necessary to reproduce the information already included in the EU application form, but it shall indicate where that information is listed in the application dossier.
Compliance with regulation	
Proof of payment of fee	
Deferral publication dates	
MSCs section	
Member State Concerned	This section requires information on member states involved, subjects included in the clinical trial from each MS, and indication of the proposed Reference Member State (RMS).
Part I – Trial specific information	
Trial details	
Trial identifiers	Proposed Full title and Public title.
Trial information	The information might include the following: · Trial category: phase and justification for whether it is a low-intervention trial or not. · Medical condition: therapeutic area being addressed. · Main objective: trial scope. · Eligibility criteria: inclusion and exclusion criteria. · End points: primary endpoints. · Trial duration: estimated recruitment start date and estimated end of trial date. · Population of trial subjects: age range, gender, and clinical trial group.
Protocol information	The protocol should contain the objective, design, methodology, statistical considerations, purpose, and organization of the clinical trial. This incorporates the following documents: · Protocol · Protocol synopsis · Data safety monitoring board (DSMB) · Study design
Scientific advice and Paediatric Investigation Plan (PIP)	This section should include a copy of the summary of scientific advice provided by the agency. If the clinical trial is part of an agreed PIP, it should contain a copy of the agency's decision on the PIP agreement and the opinion of the Paediatric Committee.
Sponsors	
Contact point for Union	The following contacts from the sponsor should be included: · Contact point for Union. · Scientific Contact Point. · Public Contact Point.
GMP compliance	GMP certificate of the manufacturer.
Products*	
Role	Indicate whether it is a test drug or an auxiliary drug.
Dosage and administration details	Dosage indications include the route of administration, maximum duration of the treatment, maximum daily dose allowed and total dose unit of measure.
Information about the modification of the medicinal product	Applicable when the medicinal product has been modified concerning its Marketing Authorisation.
Investigator brochure (IB) for the medicinal product	This document is dedicated to investigators to ensure their understanding and compliance with the key features of the protocol, including the dosage,

	administration schedule, method of administration, and safety monitoring procedures.
Investigational Medicinal Product Dossier (IMPD)	The IMPD comprises the following sections: · Quality data. · Non-clinical pharmacology and toxicology data. · Overall risk and benefit assessment. · Data from previous clinical trials and human experience.
Content labelling	The description of the content for the labelling of the IMP should comply with Annex VI of Regulation (EU) No 536/2014. The minimum required information for the label includes: · Name, address, and telephone number of the main contact for information. · Name of the substance. · Pharmaceutical form, route of administration and quantify of dosage units. · Clinical trial reference. · Batch or code number identifying the contents and packaging operation. · Subject identification number. · 'For clinical trial use only', or similar statement. · Storage condition and period of use. · Symbols or pictograms
Part II - Country specific details**	
Trial sites	
Documents	
Recruitment arrangements	Unless described in the protocol, a separate document detailing the procedure for inclusion of subjects should be provided. In case where subject recruitment occurs via advertisements, copies of the advertising material shall be submitted. For specific templates, refer to 'Part II application document templates', available under Chapter I of Eudralex vol.10.
Subject information and informed consent form	The information provided to the subjects (or their legally designated representatives) before their decision to participate or abstain from participation, along with the form for written informed consent and should adhere to national requirements.
Suitability of the investigator (per trial site)	A list of the planned clinical trial sites, name, and position of the principal investigator (CV), declaration of interest and planned number of subjects at the sites.
Suitability of the trial sites facilities (per trial site)	A justified written statement on the suitability of the clinical trial sites adapted to the nature and use of the investigation medicinal product. Description of the suitability of facilities, equipment, human resources, and description of expertise.
Proof of insurance cover or indemnification	A guarantee shall be submitted.
Financial and other arrangements	Description of the financing of the clinical trial. Whether applicable, compensation paid to subjects and investigator/site for participating shall be submitted.

Table 1. Overview of the different sections and documents necessary for CTA in CTIS. Documents are classified by different CTA subsection, with a brief description of the required documents. *All these sections and documents must be included for each product, categorized as test, placebo or auxiliary product. **Part II documents are required for each member state concerned that participates in the clinical trial. Table information is based on the Regulation (EU) No 536/2014 on Clinical trials on Medicinal Products for Human Use[55] and the CTIS-Sponsor Handbook[56].

IMPD/ CTD section	Requirements applicable to all ATMPs
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.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.
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 2. 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*[381,238].