Health by Advanced Therapies

# D3.2
# Strategy Paper on Regulatory Science for Advanced Therapies

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# 1. Deliverable's description (Regulatory Science)

Inadequate regulatory knowledge led to the inefficient translation of biomedical research and frequent failures in drug development. Collaborative efforts are needed to improve the understanding of regulatory sciences among academic drug developers. Especially the novel medicinal area of advanced therapeutic medicinal products (ATMPs), which represent highly diverse and complex products that require a strong knowledge of regulatory frameworks. Thus, basic and clinical scientists, as well as scientists working in the biotechnology and pharmaceutical industries, need an increased awareness of the regulatory questions that must be answered before an ATMP can be clinically translated. The field of Regulatory Science aims to fill those knowledge gaps to improve the efficacy in the clinical translation of novel ATMPs.

Although several definitions for regulatory science have been provided in the past, no universal formal definition exists. Within the novel draft on "Regulatory Science to 2025" (currently under revision after closing six-month public consultation phase), the European Medicines Agency (EMA) describes Regulatory Science as follows: "the range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine. It encompasses basic and applied biomedical and social sciences, and contributes to the development of regulatory standards and tools." [1] Both the knowledge generated in developing new tools and the tools themselves have the potential to inform a broad range of health-related advances, involving numerous diseases and conditions. Thus, Regulatory Science can be seen as a science-based decision-making process from preclinical towards clinical development.

In order to facilitate clinical development, it is essential to define risk and benefit in the most reasonable and appropriate way. Preclinical studies are the foundation for the initial and ongoing assessment of potential risks and as such, should be designed in order to realize their maximum value. The primary objective of preclinical safety evaluation studies is to provide data that clinical investigators can use to better predict adverse effects in study subjects and to help researchers design clinical studies that will minimize their occurrence. The same information will also help to guide research toward new, effective and less toxic drugs and, if harmful effects cannot be entirely avoided, to suggest means to lessen or alleviate the adverse actions.

Regulatory science does not take place only in laboratories. It involves scientific tools and information-gathering and analytical systems to study data, people, health systems, and communities. Advances in regulatory science must be fully integrated into the entire product development process. Outreach and collaborative efforts are integral to predicting the failure or success of new discoveries and technologies early in development and reducing product development costs. Advances in regulatory science will help make the evaluation and approval process more efficient, helping to deliver safe new products to patients faster and strengthening the ability to monitor product use and improve performance, thus enhancing patient outcomes.

To successfully achieve the mission to promote and protect public health requires the right balance between innovation and safety. Regulatory science should not stifle innovation, but rather encourage innovation while maintaining a commitment to safety and effectiveness.

In this context, the EMA recently published five main strategic goals for regulatory science until 2025. These comprise (a) catalyzing the integration of science and technology in medicines development, (b) driving collaborative evidence generation and improving the scientific quality of evaluations, (c) advancing patient-centered access to medicines in partnership with health-care systems, (d) addressing emerging health threats and availability/ therapeutic challenges and (e) enabling and leveraging research and innovation in regulatory science [2]. Herein, especially for optimizing Regulatory Science in ATMP development, the European-wide large scale research initiative of RESTORE can contribute to a large extent when aiming to reach these goals.

## 2. State of the art

The state-of-the-art regulatory framework for the classification of advanced therapies is built on various Directives, Regulations, and Guidelines, developed by the EMA, European Commission (EC), and Committee for Advanced Therapies (CAT). Medicinal products for human use in the European Union are regulated by Directive 2001/83/EC and Regulation 726/2004/EC. The regulatory term “biological products” covers a different panel of product types, including immunological medicinal products, medicinal products derived from human blood and human plasma, biotechnology products, and ATMPs. The overall classification of an ATMP as a biological product further specifies the broader regulatory framework by which the requirements of the development and the marketing authorization application are defined. These considerations are linked to the specific framework for ATMPs, Regulation 1394/2007/EC, which came into force on December 30, 2008. This regulation represents the overall framework of ATMPs. In addition, Directive 2009/120/EC updated the definitions and detailed scientific and technical requirements for advanced therapies. The class of ATMPs comprises products containing recombinant nucleic acids or engineered cells and/or tissues, without or in combination with medical devices. Consequently, these products are categorized into (a) gene therapy medicinal products (GTMP), (b) somatic cell therapy medicinal products (SCTMP), tissue-engineered products (TEP) and combined ATMPs (cATMPs).

The successful efforts in the field of Advanced Therapies, especially for gene therapies, with two CAR-T products (tisagenlecleucel (Kymriah®, Novartis) and axicabtagene ciloleucel (Yescarta®, Kite Pharma/Gilead)) being marketed successfully in both US and EU, was a result of a markedly increase in the number of academia- as well as industry-driven clinical trials [3], [4]. Thus, these approvals marked a major milestone in the field of advanced therapies. However, there are valuable lessons learned to be taken for improving clinical development and regulatory approval procedures for the next generation of advanced therapies aiming to be marketed successfully [5].

Regulatory Science needs to ensure compliance throughout the process of clinical development, and marketing authorization application in terms of quality, safety, benefit-risk assessment,

efficacy to enhance the reliability of the developed ATMP. This needs to be covered throughout the entire translational process comprising non-clinical and clinical development phases. A standard developmental pathway for a conventional medicinal product involves investigations with respect to safety in phase I, so-called First-in-human (FIH), trials in healthy volunteers. Afterward, dose-dependent safety aspects and proof of concept regarding the therapeutic efficacy and mechanism of action are assessed in phase II studies in a diseased patient, leading to final confirmatory phase III studies for efficacy in larger patient cohorts [6]. However, in the case of the novel product class of ATMPs, most of them are not susceptible to phase I studies in healthy subjects due to the rarity and severity of the disease conditions being addressed. Thus, FIH studies need to be conducted in a combinatorial phase I/IIa trial assessing safety and initial efficacy in subjects with the disease of interest. Confirmatory studies are subsequently realized in phase III or pivotal trials, where data from the latter being used to support the marketing authorization application process to relevant regulatory bodies. However, this requires an intense post-marketing authorization study and generation of real-world data to confirm and maintain the initially approved marketing authorization in the long-term (Figure 1) [7].

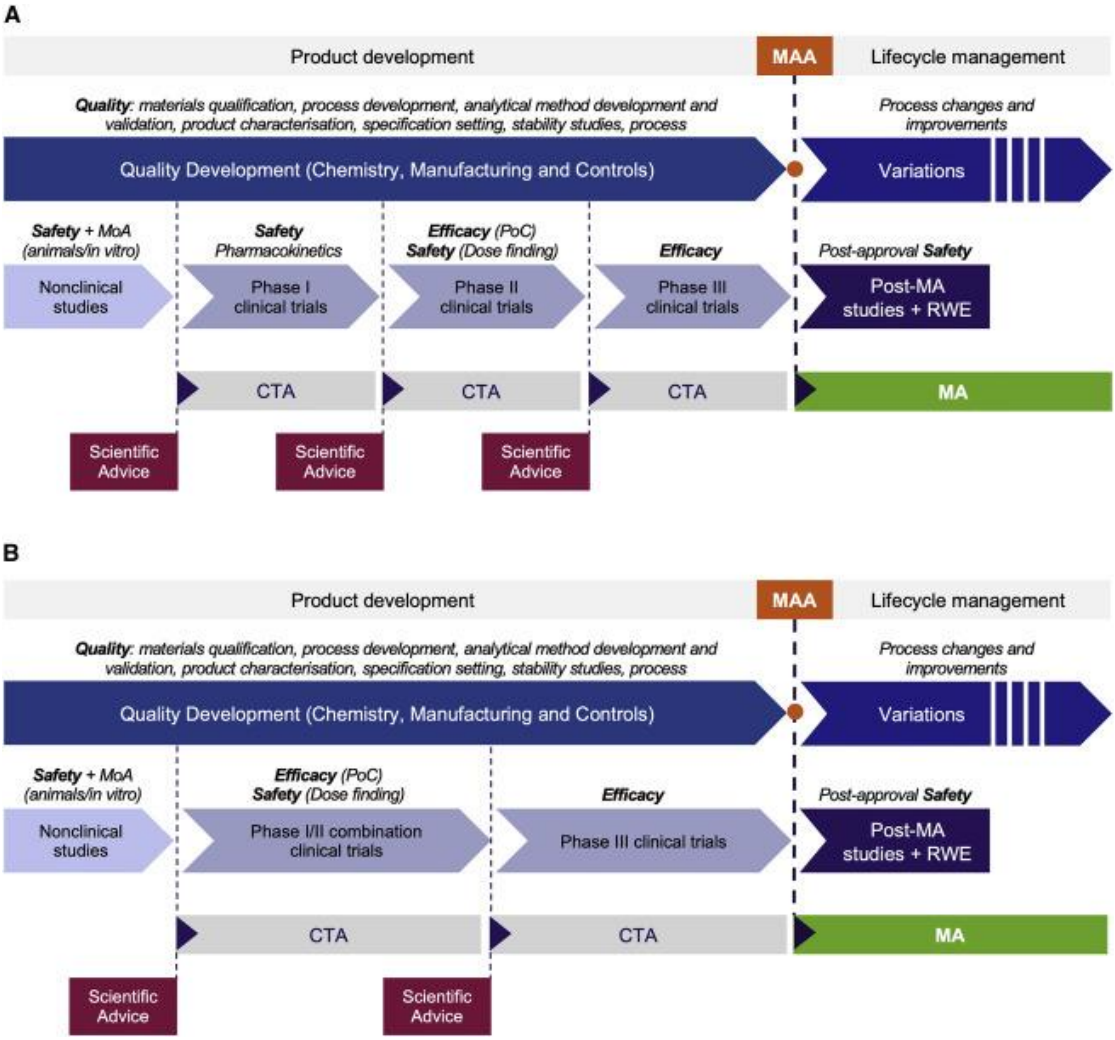


**Figure 1:** Overview on conventional medicinal product development procedures (A) versus ATMP-specific differences (B) from clinical development to marketing authorisation (adapted from Detela *et al.,* 2019 [8]).

Not only cell and gene therapy products (CGTPs) or tissue-engineered products (TEPs), but also combined ATMPs represent state-of-the-art solutions in advanced therapies that rely on special

regulatory aspects. Where an ATMP is incorporated as an integral part of the medicinal product or medical devices, the combination may qualify as a combined ATMP. An example would be tissue-engineered products that entail the seeding and culturing of differentiated somatic cells onto biodegradable scaffolds, which is then implanted into the defective or damaged sites to regenerate tissues. ATMPs are not exclusively regulated under the guidelines for medicinal products, but also under the regulatory framework of medical devices (Regulation (EU) 2017/745 and Regulation (EU) 2017/746).

In terms of advances in gene therapies, the most prominent platform currently used for genetically engineering cell and gene therapy concepts is CRISPR/Cas9-based gene editing. This tool enables researchers to precisely and permanently modify the genome of all kinds of human cells for therapeutic purposes [9], [10]. These novel delivery systems raised new regulatory questions to be addressed in terms of therapeutic applicability. This includes mainly aspects of safety, e.g. gene editing accuracy and related off-target effects, potential immune responses and immunogenicity, as well as efficiency concerns [11].

Another regulatory hurdle for gene therapy products relies on the fact that they are also classified as genetically modified organisms (GMOs). The term GMO describes an organism in which the genetic material has been altered "unnaturally" in a way that does not occur naturally by mating and/or natural recombination. This leads to additional requirements for an investigational medicinal product (IMP) that has a GMO component (Figure 2).

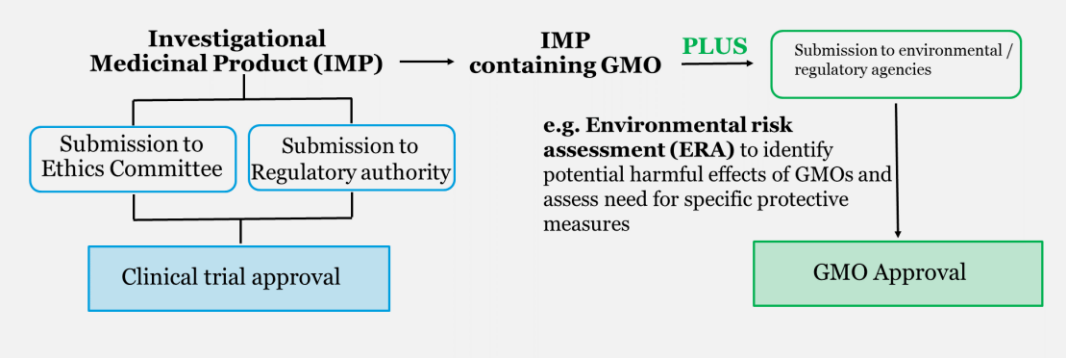


**Figure 2:** Additional regulatory requirements for GMO IMPs.

In addition to submissions to national competent authorities and ethic committees, IMPs containing GMOs must obtain a GMO approval from environmental/regulatory authorities before a clinical trial can commence. There are two main directives that gene therapy developers must comply within that context (Figure 3). The Deliberate release (DR) directive (Directive 2001/18/EC) mainly describes a GMO to be considered in wide use with fewer, or no, containment measures. The Contained Use (CU) directive (Directive 2009/41/EC) describes a GMO considered to be used in a controlled or contained setting.

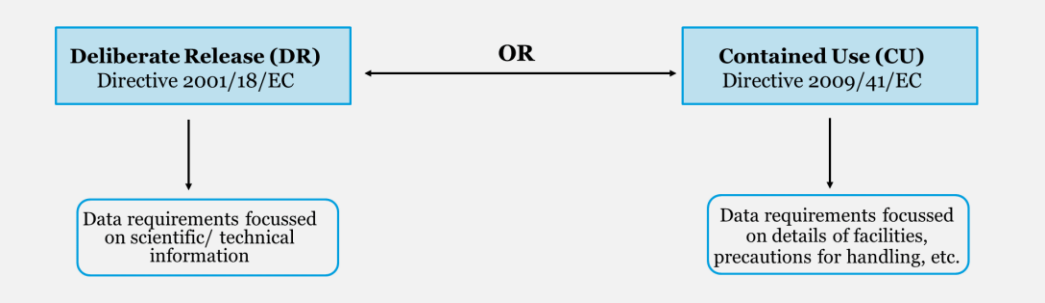


**Figure 3:** Main Directives to be compliant with under the GMO regulatory framework.

At the end of the clinical development pipeline, when it comes to marketing authorization application of an ATMP, specific regulatory pathways need to be considered (Figure 4). A marketing authorization (MA) can be granted in three ways: standard, conditional, or under exceptional circumstances depending on the extent and quality of clinical data gained during the clinical development (phase I-III) and/or whether the medicine addresses an unmet medical need or not. ATMPs for which comprehensive clinical data are never expected to be obtained will be processed via the MA under the exceptional circumstance procedure. ATMPs that qualify as orphan medicinal products and medicines under an accelerated development program may initially be processed via the conditional MA (CMA) procedure until the application can be converted to a standard MA at a later phase in the approval process. An initial CMA may also represent a feasible procedure for medicines for which a standard development program is not achievable and for which an adaptive licensing route is the most appropriate pathway. Accelerated assessment/ expedited review of standard and CMA applications represent the most appropriate pathway for priority medicines (PRIME scheme) or other medicines that clearly address an urgent unmet need [8], [12].

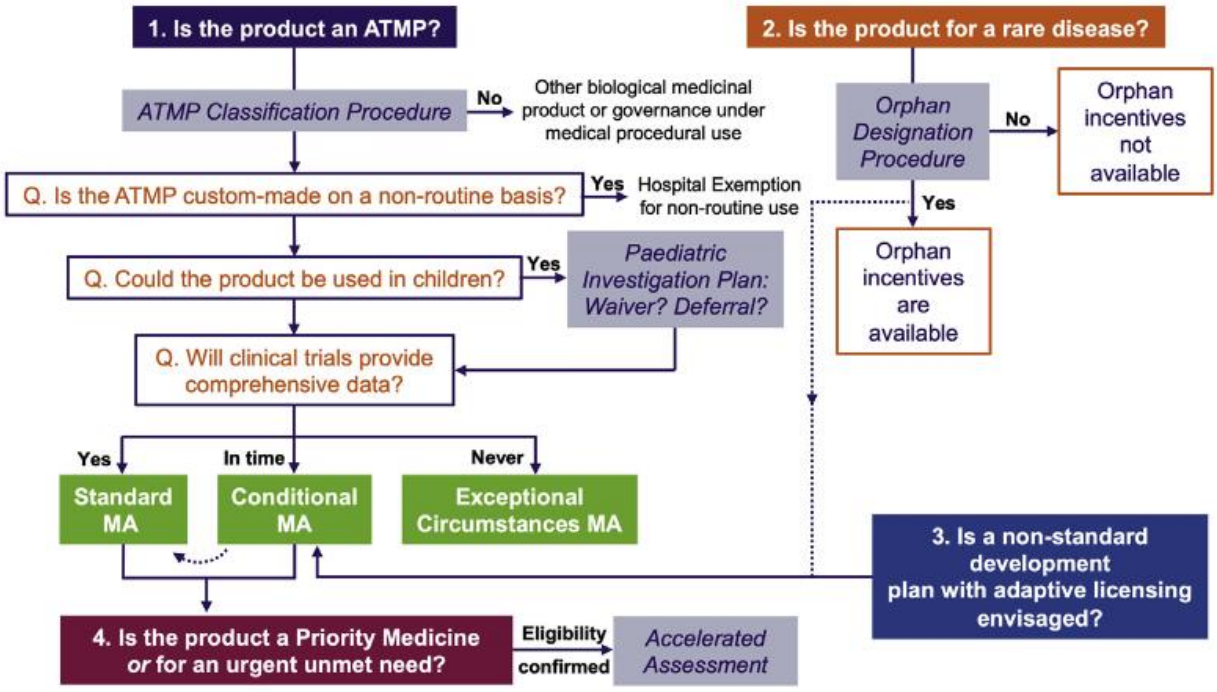


**Figure 4:** Regulatory Framework for Marketing authorisation procedures on ATMPs in Europe (adapted from Detela *et al.,* 2019 [8]).

## 3. Challenges and Limitations

The European ATMP field is still in its early stages, and developers face challenges on many levels. A European-wide survey-based cohort study among companies involved in ATMP clinical development verified the inevitable role of regulatory science in ATMP development [13]. The survey invited 271 commercial ATMP developers, of which 68 responded, providing 243 challenges. Of products in development, 72% were in early clinical development, and 40% were gene therapies. Most developers represented small- or medium-sized enterprises (65%). After classification, the top three challenge domains were related to regulatory (34%), technical (30%), and scientific (10%) challenges. Thus, clearly showing the need for regulatory science supporting the ATMP development pipeline in academia as well as small- and medium-sized enterprises [13].

For gene therapy product developers, specific challenges may include the thorough analysis of off-target activity by tools that combine in-silico and in-vitro methods, and that will be accepted by regulatory authorities. With respect to in-vivo gene editing approaches, it may be required, but also challenging, to conduct a non-clinical biodistribution study to gain information on the dissemination of the applied product. It may be expected to be difficult to fully characterize the final product with (regulatory-wise) suitable analytical assays, especially when the product's mechanism of action may not be fully understood. Another major challenge relies on the inherited variability existing in these types of products, which makes them ineligible for scalability in late-phase clinical trials. With respect to enhancing the degree of reproducibility, scalability, and standardization, bioreactors, as an emerging strategy for automated production, are also being examined intensively as means for scaling up/out manufacturing and reduce sources of contamination [14]. However, developers are still struggling to figure out the optimal regulatory pathway for these emerging manufacturing technologies. In general, developers should be encouraged to have frequent interactions with regulatory bodies to ensure gaining useful feedback on the above-discussed challenges to increase the regulatory robustness of their clinical translation pipeline.

Concerning combined ATMPs, there is a need for more clarification on the classification of combined ATMPs, especially in borderline cases, as the classification requirements can raise uncertainty. A combined ATMP is classified as such when the device element of the ATMP is an integral part of the final product and alone might be classified as a medical device. In contrast, the combined component is considered as an "excipient" if it is not or no longer used as a medical device.

Regarding the aforementioned GMO challenges, the GMO legislation is interpreted and implemented differently across the Member States, e.g., due to different definitions of GMOs as a result of a differential application of Deliberate Release and Contained use Directives. In this context, data requirements for applying required environmental risk assessments (ERA) vary in each Member State depending on which directive is being used. Herein, the Deliberate release directive focuses on data requirements based on scientific/ technical information. In contrast, the Contained use directive aims at data requirements based on the details of facilities, precautions

for handling, and other related aspects (Figure 3). Also, there are different regulatory authorities responsible for evaluating clinical trial applications (CTA) (competent authorities) and ERA (Environmental Agency), thus further complicating the regulatory framework for assessing gene therapy products. There is an evident lack of harmonization between GMO and CTA requirements. Moreover, a high degree of variability across member states in terms of timelines and regulatory procedures must be noted (Figure 5). Thus, in contrast to the FDA-regulated are in the US, where clinical trials with GMOs IMPs do not require a GMO approval procedure, GMO approvals in Europe may delay gene therapy clinical trials.

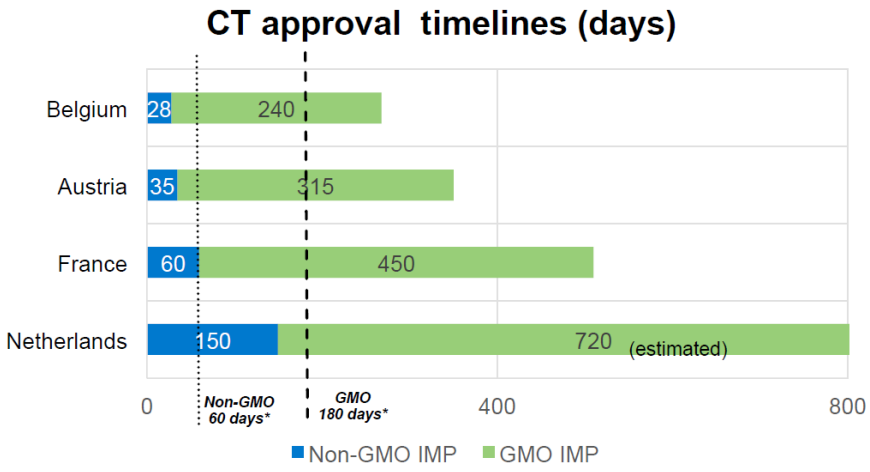


**Figure 5:** Exemplary overview on approval timelines for clinical trial applications on Non-GMO IMPs vs. GMO IMPs (Adapted from ANN GORMAN, AMGEN LTD, UK 16 DECEMBER 2016).

## 4. Putative solutions

As a complex and heterogeneous group of products, ATMPs require a strong knowledge of regulatory frameworks. Therefore, there is a clear need for dissemination of the regulatory knowledge throughout the EU, e.g., via establishing training, workshops, online regulatory support tools and educational programs. Moreover, seeking frequent and early interactions with EU and national competent authorities (NCAs) may help to attenuate regulatory challenges.

It is also essential to ensure that environmental risks from GMO-IMPs are well understood and controlled adequately. In terms of GMO legislation linked to gene therapy products, it would be important to engage the European Commission in order to achieve a universal definition of a GMO and how GMO guidance can be regulated and implemented in the Clinical Trial Regulation. Moreover, strategies need to be developed and presented for harmonization in regulatory evaluation timelines and data requirements wherever possible. Herein, it would be of importance to realize this with national agencies to ensure the new Clinical Trial Regulation is not compromised. Overall solutions should focus on interacting with the European Commission to produce a panel of requirements and work with regulatory agencies and member states to encourage convergence.

With reasonable scientific evidence gathered and analyzed, a mutual agreement can be reached to close existing gaps among researchers, developers, clinicians, patients, and regulatory bodies in multi-center trials or decentralized approaches. By practicing diverse, innovative regulatory, scientific research, academia has the potential to become one of the main drivers of communication. Strengthening regulatory science in the academic field may increase the awareness of the questions to be answered during ATMP development among all parties involved. Especially for gene-edited products, short-term solutions within the RESTORE consortium should rely on exploring the regulatory suitability for novel and reliable biological control tests that can demonstrate efficacy, specificity, and safety (incl. off-target effects) in the targeted tissue. For combined ATMPs, there is a need to establish further guidance on the handling of borderline and combined ATMPs to enable a transparent and predictable classification process.

Establishing regulatory support units in academia may help to achieve the proposed solutions. Setting up such academic "hubs" at the major European biomedical research campuses would centralize and support the workforce engaging in the practice of the regulatory sciences.

## 5. Challenges for RESTORE

The large scale initiative RESTORE needs to develop joint strategies for tackling the regulatory challenges of ATMPs, particularly combined products and gene-edited products, as well as GMO-containing IMPs, on a European-wide level. RESTORE should focus on establishing, in the long term, regulatory hubs throughout Europe to facilitate the collaboration and reduce the communication barriers among the regulatory agencies, academia, and industry. Another main challenge to be solved is exploring the regulatory suitability for novel and reliable biological control tests that can demonstrate efficacy, potency, specificity, and safety and its harmonization in various areas of ATMP development throughout Europe. Moreover, RESTORE should engage with the European Commission in order to identify and discuss critical regulatory issues and uncertainties associated with TEP and gene editing products as well as to determine the need for additional GMO legislation for ATMPs.

## 6. Summary

Regulatory Science can play a major role in optimizing ATMP clinical development by creating common strategies for tackling the regulatory challenges such as the ones seen in gene-edited products/ gene therapy, tissue-engineered products, and combined ATMPs. Creating academic regulatory hubs can be seen as a mean to achieve this goal.

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