ENGLISH | MARCH/2023

An overview of the regulatory framework for advanced therapies

Regulatory Affairs Workgroup

sindusfarma

Declaration of interest

SINDUSFARMA is an association that represents the interests in public and private affairs of pharmaceutical companies operating in Brazil. This includes actively collaborating on the development of a regulatory environment that enables our members to develop and deliver therapies within the Brazilian market and in other markets.

Keywords

Advanced therapy medicinal products; regulatory affairs; regulatory science.

Introduction

The present work has the objective to introduce the current worldwide regulatory scenario for products that fall into the category of advance therapies. First, there is a need to better understand which type of product can be considered an advanced therapy medicinal product (ATMPs):

- According to European Medicines Agency (EMA), "advanced therapy refers to new medical products that use gene therapy, cell therapy, and tissue engineering. They can be used to treat diseases or injuries, such as skin in burns victims, Alzheimer's, cancer, or muscular dystrophy, and have huge potential for the future of medicine".
- According to the US Food and Drug Administration, regenerative medicine therapy is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products. This definition excludes low risk products which are subject to different regulation.
- Per Brazilian Health Regulatory Agency (Anvisa), the possibility of manipulating human cells and genes has led to the development of new therapeutic products, the so-called advanced therapy products, which can be used to treat, prevent, or diagnose a disease with little or no therapeutic alternative.

This presents detailed regulatory requirements and available regulations from countries and regions that already have an established framework, being Argentina, Brazil, the European Union (EU), and the United States (US). The categories in scope of this work are: Regulatory classification, product categories, packaging, product insert requirements, good manufacturing practice (GMP), pharmacovigilance, environmental safety evaluation, clinical trial application (CTA) and investigational new drug (IND) application, post-approval changes, chemistry, manufacturing and controls (CMC)/Quality, importation process, prioritization pathways, transport validation, local release testing and traceability.

Considering that advanced therapies have advanced in their clinical development relatively recently and there is still much to learn from these products, from new technologies arising, and patient needs, this paper contains important information about how such products are regulated - from clinical trials, regulatory registration and lifecycle management - from the point of view of Agencies from the countries and regions that are scope of this work. Being a new topic that still requires further understanding on nature and risks of products, specific requirements, long-term exposure, among others, it is highly recommended, where there is a viable option, to engage with the Agencies prior to clinical trial design and/or marketing authorisation application to get concurrence on what is expected in regulatory terms.

It has an educational purpose with the goal to make possible the target audiences, that can be

either Agencies, companies, or individuals, to understand where we are in terms of regulatory maturity and understanding across several countries and regions, including those considered world references such as the US Food and Drug Administration (FDA) and European Union's EMA and the great experience from Italy[1], that over the last decade made a significant contribution to this field.

Regulatory classification

Advanced therapies brought a new perspective into the regulatory environment due to the high complexity of products. Countries that established this new regulatory framework have defined different classifications based on the nature of the products.

Most health authorities (HAs) have classified advanced therapy products as biological medicines, including the EMA[2] (REGULATION (EC) No 1394/2007) and Argentina's Administácion Nacional de Medicamentos, Alimentos y Tecnologia Médica (ANMAT)[3,4] 179/18, ANMAT 7075/11; 2nd article).

In the case of the US these products traditionally have been considered biologics or combination products, and only since 2016 these products have been defined as regenerative medicine therapy[5]. (Section 351 of the Public Health Service Act).

On the other hand, ANVISA[6], through the Resolution of the Collegiate Board (RDC) 338/20, included these products in a new special classification.

Categories

When discussing about possible categories of these products, considering the huge number of advanced therapies that can be developed, there are countries which further divide for advanced therapies into categories based on risk class or nature of the product. This is the case of Brazil and the US, while Argentina and European Union (EU) have no specific categorisation.

In Brazil, ANVISA[6] defined two classes of advanced therapies through RDC 338/20 on its 6th Article, I and II, as follows:

- Class I: advanced cell therapy product submitted to minimal manipulation and that performs in the receiver a different function from the one performed in the donor.
- Class II: product subjected to extensive manipulation, tissue engineering product and gene therapy product.

FDA also defined separate categories for human cells, tissues, cellular and tissue-based products, as stated in Guidance for Industry and FDA Staff - Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue Based Products: Minimal Manipulation and Homologous Use (July 2020)[7]. These specific products are divided into Lowest, Middle and Highest-tier products:

- Lowest-tier products - cells and tissues are transplanted as part of fertility treatments.
- Middle-tier products - minimally manipulated, homologous use, not combined with other substances and no systemwide effect.
- Highest-tier products - not meet the criteria for the low or middle tier.

Packaging requirements

In general, packaging requirements are not specific to gene therapy products and will depend on the nature, use and characteristics of each product. Although it is product dependent, EU guide-

line[2] indicates high level points to be considered, such as traceability when product is indicated for autologous use.

In Brazil and, Argentina there is no specific regulation or guideline regarding primary and secondary packaging requirements for advanced therapies and neither does it exist in the US for regenerative medicines, however, it is worth mentioning that these agencies have specific labeling requirements, including packaging, applicable to all product types.

Product insert requirements

One important topic for this complex set of products is the definition of minimum warnings and essential information required in the labeling text to ensure the safe and correct use of each product. Although this is a quite new topic and further experience with this class of products is still required, Agencies like EMA are opening the doors for companies to align the text validation with them prior the product registration. Argentina may follow the same approach as they are aligned with EU on this topic.

In US and Brazil there is no specific guidance or regulations for labeling warnings of regenerative medicines and advanced Therapy Products respectively, but its foreseeable that it may also be defined along the respective Agency considering the particularity and complexity of these category. Important to mention that even though there are no specific regulations for labeling of these types of products, there are specific labeling requirements well established. In the US there are labeling warnings defined in the Physician Labeling Rule, such as Boxed Warning and Warnings and Precautions that have been applied to approved advanced therapies.

US may have more experience with this working directly along companies on the definition of requirements, but in Brazil as this is such a new topic, it may require familiarity with the products.

Another point for consideration is the inclusion of information of product origin, mainly for cell or tissue-based medicines, a topic well established in EU Directive 2001/83/EC[8]. In US FDA issued a guidance to assist the industry on the requirements for determining donor-eligibility for human cells, tissues and cellular and tissue-based products.

GMP requirements

In general, all countries in scope have GMP requirements defined for drug substance (DS) and drug product (DP) manufacturing and associate sites:

- In Argentina, the topic is included in ANMAT 179/18[3] and in the regulation for biologics ANMAT 7075/11[4] (Biologics);
- Brazil, through RDC 214/18[9], provides requirements for Good Practices in Human Cells for Therapeutic Use and clinical research, and others. In addition, the RDC 508/2021[10] defines essential requirements for all companies involved in the manufacture of a product, including all steps from cellular processing to storage, emphasizing rules for quality, physical structure and for outsourcing steps, among others;
- EMA includes the GMP requirements in Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (2017)[11] ;
- At last, US regulates the GMP requirements in Reg# 21CFR[12], part 211, where advanced therapies are included in the scope of current GMP regulation for drugs.

Pharmacovigilance requirements

All countries included in this review have Pharmacovigilance (PV) regulations that manage the local/regional systems, however only US and Europe have specific documents for advance therapy registration and human gene therapy products respectively that provide guidance and regulations regarding safety, pharmacovigilance, including specifically the long term follow/up activities, specific committees for creation and how to handle adverse events/reactions. There is a trend to review it during regulatory process and risk management plan (RMP) discussions and it is possible to have specific guidelines creation for advance therapies in other HA agencies.

EU, with Procedural Advice on the Evaluation of Advanced Therapy Medicinal Products in accordance with Article 8 of Regulation (EC) No 1394/2007[2] describes rules for registration and pharmacovigilance/monitoring actions after regulatory approval. The main points of this regulation relates to the need to present follow-up monitoring actions, risk management plan after regulatory approval, creation of a committee to review advance therapies products and the need to follow directions in case critical adverse events or reactions be notified.

In Argentina there is no specific local regulation for PV monitoring related to advanced therapies, so the regulation for synthetics/biologics should apply.

Brazil´s ANVISA recently published RDC 406/2020 that establishes Pharmacovigilance rules, however there is no specific item/topic related to advanced therapies.

In the US there is the Guidance for Industry - Long Term Follow-up After Administration of Human Gene Therapy Products (Jan 2020)[13] about patient follow up clearly states that the duration of long term follow up protocols should be sufficient to observe the subjects for risks that may be due to the characteristics of the product or the nature of the exposure. Recommendations for the duration vary from 5-15 years depending on the product type, however it is related to long term follow-up and applies only to the period of a clinical trial.

Environmental Safety Evaluation (GMOs)

EMA

In November 2021[14], EMA updated its procedural advice on the evaluation of ATMPs, in accordance with Article 8th of Regulation (EC) No 1394/2007. This updated guidance details the roles and responsibilities of the three of EMA's scientific committees involved in the evaluation:

- Committee on Advanced Therapies (CAT)
- Committee for Medicinal Products for Human Use (CHMP)
- Pharmacovigilance Risk Assessment Committee (PRAC).

As provided in the ATMP Regulation (EC) No 1394/2007[2], the scientific evaluation of Marketing Authorisation Applications (MAAs) for ATMPs is primarily performed by the Committee for Advanced Therapies (CAT). The CAT prepares a draft opinion on the quality, safety and efficacy of each ATMP subject to marketing authorisation application (MAA), which is sent for final approval to the Committee for Medicinal Products for Human Use (CHMP). The CHMP recommendation is then sent to the European Commission (EC), which adopts a decision binding in all Member States.

In case a medicinal product for human use contains or consists of genetically modified organisms (GMO), the CAT (Co-)Rapporteurs shall take into consideration comments received from the

consultations with national competent authorities designated under Article 4th(4) of Directive 2001/18/EC (GMO competent authority)[8].

US

Three federal agencies within the U.S. government work together to regulate most GMOs their safety for human, plant, and animal health. These agencies also monitor the impact of GMOs on the environment[14].

- The U.S. Food and Drug Administration (FDA): regulates most human and animal food, including GMO foods.
- U.S. Environmental Protection Agency (EPA): responsible for protecting human health and the environment, which includes regulating pesticides.
- U.S. Department of Agriculture (USDA): protects agriculture in the United States against pests and disease. Animal and Plant Health Inspection Service (APHIS) sets regulations to make sure GMO plants are not harmful to other plants.

The Coordinated Framework for the Regulation of Biotechnology[15] established in 1986, describes how the agencies work together to regulate GMOs.

This guidance applies to sponsors developing human gene therapy (GT) products intended to treat a rare disease in adult and/or pediatric patients regarding the manufacturing, preclinical, and clinical trial design issues for all phases of the clinical development program.

According to this Guidance, sponsors are strongly encouraged to contact the Office of Therapeutic Products (OTP) in the Center for Biologics Evaluation and Research (CBER) prior to investigational new drug application (IND) submission and during product development. This assessment may include product-related variations (e.g. impurities such as empty and wild-type viral particles in viral vectors; variability in genetically modified cell therapies), potency assays, development and validation of manufacturing processes – however, the Guidance does not provide specific recommendation in regards to environmental concerns and their evaluation.

Recommendation to contact the OTP early in the product development is also stated by other specific Guidances, such as the Guidance for Human Gene Therapy for Retinal Disorders[16] and the Guidance for Human Gene Therapy for Hemophilia[17], both issued in January 2020 by the Center for Biologics Evaluation and Research. However, as noticed for the Guidance for Human Gene Therapy for Rare Diseases, there is no specific recommendation for environmental impact evaluation.

ANVISA

Brazil's Resolution RDC n. 505/2021[18] and RDC n.338/2020[6], which establishes minimum requirements for the registration of advanced therapy products, does include the definition of the National Technical Commission on Biosafety (CTNBio):

"A multidisciplinary advisory and deliberative collegiate body to provide technical support and advice to the Federal Government in the formulation, updating and implementation of the National Policy on Biosafety of GMOs and their derivatives, as well as in the establishment of technical safety standards and technical opinions regarding the authorisation of activities involving research and commercial use of GMOs and their derivatives (construction, experimentation, cultivation, handling, transportation, marketing, consumption, storage, release and disposal), based on the assessment of their zoo-phytosanitary risk, human health and the environment;"

According to the Brazilian regulatory framework, the Advanced Therapy Products (ATP) involving GMOs cannot be marketed in the Country without the official positioning of CTNBio, as per Law 11.105/2005[19]. CTNBio evaluation can be done either prior or in parallel to the Marketing Authorisation (MA) evaluation performed by the Office of Blood, Tissues, Cells and Organs GTSCO-ANVISA, but the marketing of the approved drug can only happen after the approval of both GTSCO-ANVISA and CNTBio.

Evaluation of post-marketing authorisation monitoring activities is also part of CNTBio evaluation. Routine pharmacovigilance activities may be accepted, considering the approval granted for Luxturna® (Novartis) in 2020 in Brazil[20].

ANMAT

Advanced therapies are framed by regulation n. 179/28[3], which in turn makes reference to regulation n. 7075/11[4] to define cells and gene therapies as biologic drugs.

However, both regulations do not include any specific requirement for environmental safety evaluation, nor a specialized Committee that would be responsible for the evaluation; on the other hand, the environmental assessment is already predicted for the agricultural sector, as defined by Resolution 763/2011[21].

Clinical trial design

Preclinical and clinical trials expected design and requirements are a key topic for consideration when we talk about advanced therapies. As stated, the diversity of products that may be developed based on advanced therapies impose a significant challenge to the development and execution of pre-clinical studies and clinical trials. In general, Regulatory Agencies are learning from the incoming products, and much is still to be defined and properly regulated, but we see that the US and EU have well stablished requirements to start with.

The EU, through the guidance of good clinical practice (GPC) specific to advanced therapy medicinal products (2019)[22] have specific and comprehensive guidelines for designing and conducting clinical trials. Argentina follows EU guidelines.

US, based on the following guidance, established a very comprehensive guide for companies to design and conduct preclinical and clinical trials for advanced therapy products:

- Preclinical: Preclinical Assessment of Investigational Cellular and Gene Therapy Products; Guidance for Industry, November 2013[23]
- Clinical: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry[24]
- Human Gene Therapy for Rare Diseases: Draft Guidance for Industry[25]
- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products[26]
- Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial[27]

Brazil regulation[6] describes the responsibilities and requirements for CTA submission, but there is nothing specific on how to design and conduct the trials with this specific class of products, so companies should rely on GCP guidelines.

Post-approval

Currently we are still in a learning curve with regards to initial registration of ATMP considering the diversity of products, so post-approval is not yet a topic fully regulated. It is certainly a topic for further discussion and that requires more kno-

wledge on the nature, complexities and specificities of each product categorized as advanced and gene therapy.

Currently post approval changes in ATMP are only regulated in EU according to EU post-approval guideline for medicinal products - Commission Regulation (EC) No 1234/2008[28]. In Argentina, Brazil, and the US there is no specific guidance for these types of products however there are clear post-approval requirements and guidelines that apply to all products including advanced therapies.

Quality

EMA

The EMA recently updated the Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells[29], which provides guidance for the development and evaluation of medicinal products containing genetically modified cells intended for use in humans. The quality section addresses both the requirements specific to the genetic modification of the target cell population and to the genetically modified cell product resulting from the manufacturing process.

Since its first publication, the quality section has been updated due to the evolution of science and regulatory experience, with an emphasis on starting materials, comparability, and validation.

An important point of attention regarding ATPMs corresponds to the risks posed by the administration of genetically modified cells to patients and third parties, being also addressed by this Guideline. According to it, the risk posed by the administration of genetically modified cells depends on:

- the origin of the cells;
- the type of vector;
- the method used for the genetic modification;
- the manufacturing processes;
- the non-cellular components.

Reference is made to the risk-based approach proposed by the Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC for ATMPs[8].

The risk-based approach corresponds to a strategy to determine the extent of quality, non-clinical and clinical data to be included in the MAA dossier. **Table 1** replicates an example of this approach from the guideline:

Table 1: Annex 1: Example: AAV vector expressing the human fictionase enzyme (FE) administered i.m. for the treatment of FE deficiency disease/ EMA/CAT/CPWP/686637/2011[30]

Risk / Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Toxicity resulting from unintended alteration of therapeutic gene expression
Recombination/ mobilisation	Recombination may lead to replicating AAV. Tumor formation depends on level of AAV genome integration into host genome. Addressed in CTD 3.2.P.5 - Control of FP and CTD 4.2.3 –Toxicology (toxicology/ integration studies).	Recombination / Mobilisation may lead to increased immunogenicity due to higher number of vector / RCV particles. Addressed in CTD 3.2.P.5 - Control of FP and CTD 4.2.3 -Toxicology.	Recombination during manufacture might lead to loss of the transgene and consequently loss of function. Addressed in CTD 3.2.P.5 - Control of FP.	Mobilisation (with wt virus and helper coinfection) might result in higher levels of therapeutic gene expression. Toxic effects other than immunogenicity due to overexpression is considered to be low. Addressed in CTD 4.2.1 - Pharmacology and CTD 4.2.3 - Toxicology studies, and justified by literature information.
Integration	AAV vectors are able to integrate into the genome albeit at low levels. Integration studies have been performed (CTD 4.2.3- Toxicology) and demonstrate absence of integration. See also risk factor 'biodistribution' (CTD 4.2.2 - Pharmacokinetics)			
Type of transgene and transgene expression levels		The therapeutic gene is of human origin and respective endogenous gene product in patients is present but defective. This might cause unwanted immunogenicity. Expression of therapeutic protein addressed and justified in CTD 5.3.5 -Reports of efficacy and safety studies.	Impaired transgene expression might lead to treatment failure. Transgene expression and potency studies and in vivo proof-of-concept studies. Addressed in CTD 3.2.P.5 - Control of FP and 4.2.1. - Pharmacology.	Over-expression of transgene in target cells is not considered to be of concern. Toxic effects other than immunogenicity due to over-expression is considered to be low. CTD 4.2.1 - Pharmacology, CTD 4.2.3 - Toxicity and justified by literature data.
Vector type	AAV is not known to be tumorigenic per se. A low potential of AAV for insertional mutagenesis exists (see RF 'integration'). Addressed in integration studies (CTD 4.2.3 - Toxicology). Justification of lack of tumorigenicity studies based on respective integration data.	AAV is known to be immunogenic. Addressed in immunogenicity and Toxicity studies (CTD 4.2.3), and Clinical safety studies (CTD 5.3.5 - Reports of efficacy and safety studies,).	Pre-existing immunity to the vector might impair efficiency of treatment. Furthermore repeated administration may increase immunologic responses against the vector that might also impair efficiency of treatment. Addressed in CTD 4.2.1 - Pharmacology and 5.3.5 - Reports of efficacy and safety studies.	
Impurities	Impurities might contribute to tumour formation. Full information and documentation on starting materials is given. Control of cellular and viral impurities are addressed in release testing (CTD 3.2.S.4 – Control of critical steps and intermediates, and 3.2.P.5 – Control of FP).	AAV can be difficult to purify. Amount and type of impurities may lead to immunogenic reactions. Addressed in CTD 3.2.S.2 (Manufacture), 3.2.S.4 (Control of AS), 4.2.3 (Toxicology), and 5.3.5 - Reports of efficacy and safety studies.	Impurities can negatively influence the efficacy of treatment. Addressed in drug substance control CTD 3.2.S.4 - Control of AS.	

Risk / Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Toxicity resulting from unintended alteration of therapeutic gene expression
Biodistribution	Biodistribution of the vector contributes to the risk of tumour formation via vector persistence and integration events (see risk factor on integration). Inclusion of transduced non-target organs in studies on episomal/ integrated vector status. Addressed in CTD 4.2.2- Pharmacokinetics (biodistribution), CTD 4.2.3 – Toxicology (integration studies).	Biodistribution of the vector to non- target, immunogenic sites. Addressed in biodistribution / immunogenicity studies -CTD 4.2.2 - Pharmacokinetics (biodistribution), CTD 4.2.3 - Toxicology (immunogenicity), CTD 5.3.5 -Reports of efficacy and safety studies, (clinical safety).	Treatment failure might be induced by unwanted immunogenicity due to biodistribution to non-target, immunogenic sites. Addressed in biodistribution and long-term transgene expression studies. CTD 4.2.1 - Pharmacology and CTD 4.2.2 – Pharmacokinetics.	Toxicity as a result of transgene-overexpression in non-target cells considered to be low. Evaluation of toxicity and transgene expression levels in non-target tissues and cells. CTD 4.2.2 - Pharmacokinetics (biodistribution) and 4.2.3 - Toxicology (toxicity)
Relevance of animal model		Animal model is not predictive for immunogenicity in patients due to differences in immune responses. An additional animal model to address immunogenicity was used. Addressed in CTD 4.2.3 - Toxicology (immunogenicity) and in clinical studies CTD 5.3.5 - Reports of efficacy and safety studies.	Animal model may not be predictive for treatment failure due to differences in the immune status of animal and patients. Immune status of the animal model has been matched to the patient's situation (e.g. pre-treatment with the vector to induce seroconversion in animals). See CTD 4.2.1 - Pharmacology and 4.2.3 - Toxicology.	
Patient-related		Immune reaction might be triggered dependent on immune status of the patient. Addressed in non-clinical studies using vector- pretreated animals (CTD 4.2.3 - Toxicology) and in CTD 5.3.5 - Reports of efficacy and safety studies (clinical safety)	Immune status e.g. pre-existing immunity to the vector of patient might influence efficiency of therapy. Addressed in non- clinical (CTD 4.2.1 - Pharmacology) and clinical studies (CTD 5.3.5 - Reports of efficacy and safety studies)	
Disease-related	The underlying disease might be linked to a higher incidence of cancer. This might bias the safety data. Addressed in CTD 5.3.5 - Reports of efficacy and safety studies.	Variable levels of dysfunctional protein may be expressed in the patients resulting in immune reactions to the therapeutic protein. Addressed in CTD 5.3.5 -Reports of efficacy and safety studies.	Immune response against the transgene might compromise treatment efficacy. Addressed in the non-clinical pharmacology (CTD 4.2.1) and toxicology studies (CTD 4.2.3), and in Reports of efficacy and safety studies (CTD 5.3.5).	
Medical procedure-related	Concomitantly administered immune suppressants might lead to tumour formation. Addressed in CTD 5.3.5 - Reports of efficacy and safety studies.	A high local dose administered i.m. might cause local inflammatory response due to immunreaction to a vector component or the expressed therapeutic protein. Addressed in CTD 4.2.3 - Toxicology and 5.3.5 - Reports of efficacy and safety studies.	Difficult administration of multiple injections i.m. might result in incomplete dosing. Addressed in CTD 5.3.5 - Reports of efficacy and safety studies and SmPC	

Blank box means that based on the current substantial scientific knowledge no reasonable risk factor/risk relationship exists.

The application of the risk-based approach in the preparation of a MAA dossier is optional. However, in cases where the risk-based approach is being applied, the applicant is advised to follow the methodology as laid down in the present guideline.

Regarding stability studies requirements (including in-use stability studies) reference is made to the Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)[31].

This Guideline provides an open concept for stability and specifically for Quality Control, it states that due to the complex nature of the active substance of a Cell-Based Medicinal Product (CBMP), requirements for stability should be defined on a case-by-case basis. It also proposes that, whenever possible, stability should be assessed for both the cellular as well as the non-cellular component prior to combination and together as a finished product in the final packaging.

FDA

The FDA issued two specific guidance's for chemistry, manufacturing and control (CMC), one for Gene Therapy (CMC) information for human gene therapy investigational new drug applications (INDs)[32] and the other for somatic cell therapy[33].

For the chemistry, manufacturing, and control (CMC) information for human gene therapy investigational new drug applications (INDs), the objective is to stablish the requirements to assure product safety, identity, quality, purity, and strength (including potency) of the investigational drug. It applies to human gene therapy products and to combination products that contain a human gene therapy in combination with a drug or device, following the CTD structure for the architecture of the application:

- Module 1: Administrative Information
- Module 2: Summary of Quality Information
- Module 3: Manufacturing Process and Control Information (for drug substance (DS) and drug product (DP)).

Important to mention that the FDA recognizes that distinguishing a DS from a DP may be difficult for some gene therapy products, due to the complex nature of the manufacturing processes. Therefore, the Guidance recommends the sponsor to provide an explanation to support the definition of DS/DP for the product in the summary information in Module 2 of CTD submissions. A separate DS section should be provided for vectors used for ex vivo modification of cells.

For Somatic Cell Therapy, the FDA issued a Guidance for Reviewers and Sponsors: "Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)".

According to this document, human somatic cell therapies present many manufacturing challenges:

- variability and complexity inherent in the components used to generate the final product, such as the source of cells (i.e., autologous or allogeneic),
- the potential for adventitious agent contamination,
- the need for aseptic processing,
- the inability to "sterilize" the final product because it contains living cells.

The Guidance also mentions that the distribution of these products can be a challenge due to stability issues and the frequently short dating period of many cellular products, which may require the release of the final product for administration to a patient even before certain test results are available.

Regarding the format of the dossier, the CTD format is not specified, but rather encourage spon-

sors to use the format and headings described in Appendix A to facilitate an efficient review by FDA.

Specific CMC Guideline for tissue engineered therapy medicinal products was not identified in this evaluation.

ANVISA

Resolution RDC n.338/2020[6] establishes the minimum requirements for the marketing authorisation of ATMPs, based on the proof of its efficacy, safety and quality for use and marketing in Brazil.

Chapter III of this resolution applies to all ATMPs, outlining general requirements (mainly summaries) for the technical report:

1. summary of general characteristics of the product;
2. summary with information on the mechanism of action and the clinical use of the advanced therapy medicinal product;
3. summary of production information, in order to highlight the critical parameters of product's quality;
4. summary and critical analysis of the non-clinical aspects of the product;
5. summary and critical analysis of the clinical aspects of the product.

More detailed requirements are specified in Article 23 rd of Chapter V, which is applicable for Class II drugs:

- somatic cell therapy medicinal product undergoing extensive manipulation;
- tissue engineered therapy medicinal product;
- gene therapy medicinal product;

Requirements in this article concerns mainly:

1. Starting materials, raw materials and excipients.
2. Active component and the final advanced therapy medicinal product.
3. Manufacturing steps of an advanced therapy medicinal product.
4. Protocol and report of the stability studies performed.

Despite the Article 23rd provide more detailed requirements for the manufacturing and quality control, there are no details specified for Stability Studies such as number of batches, timepoints and study design.

Importation process guidelines

Import process is fully influenced by the nature of the product, storage condition, presentation, and packaging, among other variables. This is laid down in Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products C (2017) 7694[34] states the exemption from batch controls carried out on ATMPs imported into the European Union from a third country and additional information about product testing requirements.

Argentina, Brazil and the US lack regulations for importation.

Expedited regulatory pathways

FDA: expedited pathways.

The distinct approaches to speed up the availability of drugs could be applicable to ATPMs, if criteria are met Breakthrough therapy, Accelerated Review and Regenerative Medicine Advanced Therapy designation (RMAT), fast track which are

granted during development and priority review[35] that can be requested at the time of the original submission.

Fast track expedites the development and review of drugs to treat serious conditions and fill an unmet medical need with the potential for rolling review at the time of filing the application. On the other hand, Breakthrough Therapy pathway expedites the development and review of drugs which may demonstrate substantial improvement over available therapy. In either case, if a certain drug receives a fast track or breakthrough therapy designation, then it becomes eligible for accelerated approval and priority review, if relevant criteria are met.

Accelerated approval is requested by the company during development and granted when a drug treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint, on the other side Priority review also requested by the company at the time of original NDA/BLA submission and is granted when an application treats a serious condition AND if approved provides significant improvement in safety or efficacy OR is a supplement that provides a labeling change based on a pediatric study.

Either fast track or breakthrough therapy are also requested by the company. For the fast track, the request can be initiated at any time during the drug development process; for the Breakthrough Therapy designation, request should be received by FDA no later than the end-of-phase-2 meetings. In both cases, it is expected a response from FDA within sixty days.

Neither of those approaches require an Orphan Drug designation prior to the request. The Orphan designation is a standalone process which qualifies the sponsor of the drug for various development incentives of the orphan drug act (ODA) such as 7-year market exclusivity, tax credits and other incentives[36], but does not alter the standard regulatory requirements and process for obtaining marketing approval[37].

EMA: PRIME scheme and accelerate assessment

The European Medicine Agency has developed a specific scheme for the development of medicines that target an unmet medical need, which is known as PRIME[38].

PRIME scheme supports early dialogue and scientific advice, ensuring that patients only participate in trials designed to provide the data necessary for an application, making the best use of limited resources. Developers of a drug that benefitted from PRIME could be also eligible for the accelerated assessment at the time of application for a marketing authorisation.

Accelerated assessment reduces the timeframe for the Committee for Medicinal Products for Human Use (CHMP) to review a marketing authorisation application. Applications may be eligible for accelerated assessment if the CHMP decides the product is of major interest for public health and therapeutic innovation. If the CHMP accepts the request, the timeframe for the evaluation will be reduced to 150 days. This time frame will be split into 3 phases of 90+30+30 days of assessment, but in case of advanced therapy medicinal products, due to the need to include more scientific committees for the review, the 150-day timetable is split into 2 phases of 120+30 days of assessment.[39]

EMA updates the list of all products granted access to the PRIME scheme on a monthly basis.

ANVISA

Prioritization of submissions are already part of the specific regulation for ATMPs in Brazil (RDC

505/2021) and any medicine that meets one the criteria below will be eligible for a priority review[12]:

- be used in the treatment of rare, neglected, emerging or reemerging disease, in public health emergencies or in seriously debilitating conditions and in situations in which no alternative therapeutic is available.
- be subjected of a new therapeutic indication or of extension of use aiming the pediatric population.
- phase I or II clinical trials conducted within the Brazilian national territory.

For both class I and class II ATPMs, upon receipt of the documentation related to marketing authorisation application, ANVISA will have 120 days for a response if the ATPM fulfills the requirements for a priority review.

ANMAT: special condition

Besides the Dispositions 179/28[3] and 7075/11[4], which define cells and gene therapies as biologic drugs, the marketing authorisation could be also requested under a specific procedure known as Special Condition.

The Special Condition is established by the Disposition 4622/12 and is applicable for any drugs that met the criteria described in the Annex 1: medicines for rare diseases (prevalence of 2 or less cases in 2000) or for serious illnesses with risk of death and / or serious disability. Timeline for regulatory review and approval may vary, but approvals under this condition would present the following characteristics:

- Initial license is granted for 1 year; renewal should be submitted 3 months before the annual expiration. At the time of renewal, HAs will determine if the product should keep under this condition or could be switched to a standard registration for 5 years.
- It requires to include a Plan for monitoring efficacy, effectiveness, and safety for the product, which includes patient informed consent form and monitoring report.
- Product will include in the packaging/label the phrase "Under special conditions".

Transport Validation

Transport validation is another topic not specifically stablished in guidelines for advanced therapies, although general requirements are listed in EU Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (2017)[11]. It mentions that for ATMP requiring controlled temperature conditions during transport and/or storage prior to administration, the sponsor should ensure there is a temperature monitor/ log data and/ or confirmation that required conditions have been met.

In the US, the guidance Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)[11] recommended for the applicant to assure and describe procedures that are in place to ensure appropriate storage and transport (as needed).

In Brazil and Argentina there is no specific regulation or guideline for transport validation.

Local release testing

There is almost no regulation nor requirement about the need of local release testing for ATMPs. This is the case of Argentina, Brazil. In the US there are general requirements for batch release and testing and it is very likely that therapies under ATMP will require the applicant to develop a batch release protocol post registration as currently happens with the biologic license applications. On the other hand,

the EU Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (2017)[11] clearly states that testing is responsibility of the manufacturer, in both centralized (single site) and decentralized (multiple sites) manufacturing.

Traceability

For products deriving from human cells and tissues, Argentina[3] and US present a general requirement on data and patient information traceability. Argentina states that the traceability system should respect the protection of natural persons with regards to the processing of personal data and the circulation of this.

In Brazil RDC 338/20[6] it is possible to find a general statement requiring identification and security mechanisms that guarantee the traceability of the product. Identification and security mechanisms that guarantee the traceability of the product are a requirement for marketing authorisation application as per RDC 505/2021[18] and the proper records that enable the Traceability of cells and Advanced Therapeutic Products must be stored in a safe, organized and easily accessible way according to RDC 508/2021[10].

In EU[5,23] there is a complete description and list of requirements for traceability of products, from donor (where applicable) to patient stating that there must be a well stablished system in place to allow complete traceability of the patient as well as of the product and its starting materials, being this essential to monitor the safety of advanced therapy medicinal products.

Conclusion

Advanced therapy medicinal products (ATMP) are a new medicinal product category comprising gene therapy and cell-based medicinal products as well as tissue engineered medicinal products. ATMP development opens novel avenues for therapeutic approaches in numerous diseases, including cancer and neurodegenerative and cardiovascular diseases. However, there are important bottlenecks for their development due to the complexity of the regulatory framework, the high costs and the needs for good manufacturing practice (GMP) facilities and new endpoints for clinical experimentation[40,41].

In **Figure 1** we see that Agencies are working and issuing several guidance and regulations to adequately regulate advanced therapy products being EU one of the most advanced Health Authority on this matter, however there is still a long way to go to properly capture all complexities and diversities that may arise from this product class, specially in Latin America. Clearly there is much more to come.

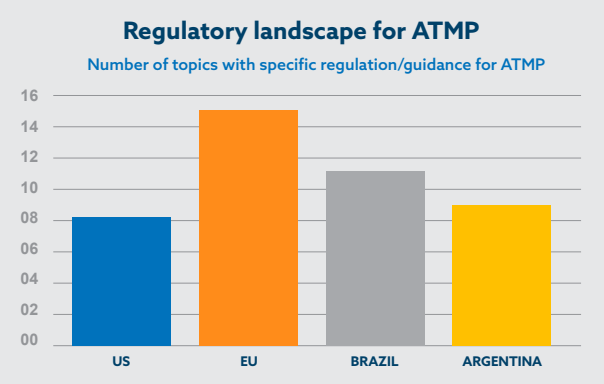

Figure 1: Regulatory landscape for regulations/guidance related specific to ATMP.

The absence of specific regulation/guidance for a topic doesn´t imply that it is not regulated by the Health Authority. There may be general regulations/guidance for drugs that apply.

Based on this it is crucial to establish a strong cooperation between all parts involved (e.g pharmaceutical companies, health authorities, trade associations) leading to the development of a robust and complete regulatory framework in Latin American region.

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