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Advanced Therapy Medicinal Products: an introduction to risk management

Produtos de Terapias Avançadas: uma introdução ao gerenciamento de riscos

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ABSTRACT

Introduction: Advanced therapy products include gene therapy, somatic cell therapy, and tissue engineered products that promise important health benefits. These products contain active cells or genetic constructs that exert a mechanism of metabolic, immunological, genetic or pharmacological action. **Objective:** To discuss main risks involved in advanced therapy medicinal products to understand risk management regulatory models and practices. **Method:** Review in the scientific literature and in official documents of the regulatory agencies of the United States and Europe. **Results:** Advanced therapy products can be difficult to define, particularly cell-based products. Completely elucidating the mechanisms of action contributes to mitigate risk of development and characterization, including through the development of disease models or other functional assays. Disease severity, predicted benefit level and safety profile will affect the number of participants and other design aspects of each test. They present a high degree of technical complexity and substantial challenges to their manufacture. **Conclusions:** Major regulatory agencies demonstrate efforts to establish clear rules for the preparation of advanced cellular products compatible with Good Manufacturing Practices and the conduct of clinical trials in order to rationalize requirements adapted to the specific characteristics of advanced therapy medicinal products.

KEYWORDS: Cell Therapy; Good Manufacturing Practices; Clinical Trials; Risks; Health Surveillance

RESUMO

Introdução: Produtos de terapias avançadas compreendem três categorias: produtos de terapia celular avançada, de engenharia tecidual e de terapia gênica, que prometem benefícios importantes para a saúde. Estes produtos contêm células viáveis submetidas a manipulação extensa ou construções genéticas, as quais possuem a finalidade de obter propriedades terapêuticas ou preventivas através de mecanismo de ação de natureza metabólica, imunológica ou farmacológica. **Objetivo:** Discutir os principais riscos envolvidos na produção e fornecimento dos produtos de terapias avançadas na perspectiva de desenvolver práticas regulatórias de gerenciamento de risco. **Método:** Revisão da literatura científica e documentos oficiais das agências reguladoras dos Estados Unidos e Europa. **Resultados:** Compreender os possíveis mecanismos de ação dos produtos de terapias avançadas contribui para mitigar riscos de desenvolvimento e caracterização, inclusive através do aperfeiçoamento de modelos clínicos ou outros ensaios funcionais. Raridade da doença, grau de benefício previsto e perfil de segurança afetarão o número de participantes e outros aspectos de design de ensaios clínicos. Este tipo de produto apresenta alto grau de complexidade técnica e desafios substanciais para sua produção. **Conclusões:** As principais agências reguladoras demonstram esforços para estabelecer regras claras de produção dos produtos de terapias avançadas, segundo as Boas Práticas de Fabricação e a realização de ensaios clínicos de forma a racionalizar requisitos adaptados às características específicas dos referidos produtos.

PALAVRAS-CHAVE: Terapia Celular; Boas Práticas de Fabricação; Ensaios Clínicos; Riscos; Vigilância Sanitária

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INTRODUCTION

The use of parts of the human body as therapeutic products is an old and heavily regulated clinical practice. The term "transplant" is used to denote any surgical act to obtain cells and withdraw organs, tissues, or parts of a living or dead body for infusion or implantation into a recipient. As Catão (p. 202)[1] explains, [...] "In general, transplants are classified in the surgical field, mainly aimed at safeguarding the biological compatibility between donor and recipient." According to the World Health Organization (WHO)[2,3], human transplant cells and tissues represent a therapeutic class that is essential to human health and capable of restoring and maintaining the vital functions of the recipient/patient. Furthermore, human cells and tissues have become an important starting material for more complex biotechnological products.

According to a report by the Brazilian Ministry of Health[4], 16,636 corneal transplant procedures and 2,362 bone marrow transplants were performed in Brazil in 2016. The same report describes Brazil as the second country that most transplants solid organs, like kidneys (5,492 transplants in 2016) and livers (1,880, 2016), after the United States only. The report of the Brazilian Association of Organ Transplants (ABTO)[5] showed that, in 2016, 16,293 human bone grafts were performed in the states of Rio de Janeiro, São Paulo and Rio Grande do Sul. If we add these data to the estimates of blood transfusions in Brazil, approximately 3 million procedures carried out in 2015[6], we can understand the importance of blood components, tissues, cells and human organs for public health, as well as the challenges of regulators to ensure the quality and safety of these products.

Scientific progress and advances in the biotechnology sector have led to a new age, known as the era of regenerative medicine, which employs products to replace or regenerate human cells, tissues or organs for the purpose of restoring or establishing an individual's normal function. According to Mason and Dunnil[7], by definition, regenerative medicine is an opportunity for all major clinical specialties to use products like medical devices, small and complex biological molecules (medicines), as well as therapeutic products consisting of or based on human cells[8], with or without their recombined genetic material, as well as organized into *in vitro* human tissues.

In this context, a new class of cellular products or originated from human cells has been considered, worldwide, as a new therapeutic arsenal for several pathological or clinical conditions formerly without alternatives[9]. Internationally, these products are referred to as Advanced Therapy Medicinal Products (ATMP) and encompass three categories: Advanced Cell Therapy Products, Gene Therapy Products and Tissue Engineered Products, which can be combined with medical devices[10].

After 8 years of enforcement of the regulatory standards applied to advanced therapy products, according to Eve et al. (cited Hanna et al.[11]), only five products were granted registration by the European Agency by October 8, 2015: ChondroCelect for cartilage repair (2009); MACI for cartilage repair (2013), whose manufacturing was discontinued in 2014; Glybera for treatment of lipoprotein lipase deficiency - LPL (2013); Provenge for treatment of advanced prostate cancer (2013), withdrawn from the European market in 2015; Holoclar for treatment of corneal epithelial cell deficiency (2015). The regulatory authorities of the United States, Japan and South Korea have developed conditional or temporary approval mechanisms for advanced therapy products under specific circumstances. South Korea was the first country to offer conditional approvals in 2001, though not specifically for advanced therapy medicinal products. The Korea Food and Drug Administration (KFDA) has authorized 18 advanced therapy products since 2001, most of them temporarily. Japan's Regulatory Agency, Pharmaceuticals and Medical Devices Agency (PMDA), also adopted conditional approval in its legislation, in order to authorize advanced therapy products by proving their safety and likely efficacy (efficacy data from Phase II studies), therefore, the respective products should still be submitted to Phase III studies to confirm their efficacy.

Taking into account the world scenario and the development of advanced therapy products, the present study aims to discuss the main health risks involved in the production and supply for therapeutic use of advanced therapy products, with a view to understanding models and regulatory practices adopted by the main regulatory agencies in the process of managing these risks.

METHOD

A bibliographic review was conducted in the following online databases: Lilacs, SciELO and PubMed, by searching for the terms "*advanced cell therapy*" and "*Advanced Therapy Medicinal Products* (ATMP)" in English and "terapia celular" in Portuguese, in papers published between 2000 and 2017. The initial selection considered the titles and abstracts of the original papers of interest to the work, indexed in the period of study. Scientific papers that addressed some type of regulatory study or risk analysis related to advanced therapy medicinal products were analyzed in their entirety and included in the work process. The vast majority of the papers found outlined clinical or experimental studies and, thus, were excluded. We also considered the official documents published by the Food and Drug Administration (FDA) of the United States, and the European Medicines Agency (EMA) of the European Community, as well as the Japanese Agency for Products and Medicines (PMDA), available on their websites in fields dedicated to advanced therapy products.

This study included 32 papers and 19 official documents organized in order to contain the description of information related to the concepts and characterization of the risks involved in some of the stages of the development process and the use of advanced therapy products. The mentioned description was arranged in a Microsoft Excel spreadsheet to facilitate the analysis of the data.

RESULTS AND DISCUSSION

In the regulatory context, from the analysis of the normative framework adopted by the United States, we observed that

the regulatory requirements defined by the FDA for advanced therapy products take into account whether the cell or tissue is "minimally handled" or "more than minimally handled". Minimal manipulation typifies processing that does not significantly alter the primary biological characteristics of the cells or tissues, such as, for example, density gradient sorting, selection, centrifuging and cryopreservation. All cell or tissue manipulation processes with the potential to alter any of its relevant biological characteristics, including differentiation and activation status, proliferation potential and metabolic activity - such as laboratory culture with objective of expansion, differentiation or genetic modification - are considered to be more than minimal manipulation, thus requiring specific controls[12]. Furthermore, another condition that supports the requirement for differentiated controls is the combination of cells or tissues with another component or device, except water, crystalloids or sterilizing, preserving or storage agents. The mechanism of action of the product also attracts regulatory attention when it suggests or confirms the execution of its primary function through an effect that is systemic and dependent on the metabolic activity of viable cells; or if the intention is reproductive use[13]. In short, it can be seen from the analysis of US regulations that, irrespective of the classified approach, advanced therapy products should be handled according to good practices guidelines for biological products[13]. Those submitted to more than minimal manipulation must also comply with specific regulatory rules.

In the same direction as the Americans, the European Union (EU) proposed an action plan that defined advanced therapy products as a category of medicines subject to the same scientific and regulatory criteria as those defined for any medicine and health product, which means that they must also have approved clinical research and supply conditioned to the registration of the product with the regulatory body[10]. According to Gálvez et al.[14], successive regulations were implemented in Europe, which defined the products of advanced therapies as biological medicines containing or consisting of viable cells or subcellular fractions with biological functions. It was therefore agreed that these products could not be included in the same categories of medicinal products or in the category of conventional transfusion, grafting and transplant products, since they: (A) contain viable human cells of allogeneic or autologous origin subjected to substantial manipulation and (B) may exhibit non-homologous use, which means that the cells are administered at body sites where they are generally not present, or perform a different biological function in the recipient than in the donor[14,15].

According to Schneider et al.[15], the definition of the typology of advanced therapy products is essential for establishing health risk mitigation requirements. The authors, through the use of the European model, classified the products into three main groups: those that are constituted by living cells submitted to processes of culture, expansion and cell optimization; tissue engineered products consisting of living cells organized into tissues or organs; and *in vivo* gene therapy products "whose therapeutic effects are achieved through the infusion in the human body of recombining nucleic acid molecules. They are therefore defined as biological medicines or products". *Ex vivo* gene therapy are those consisting of or based on genetically modified cells. These three categories of advanced therapy products could be combined or not with solid carriers or, where applicable, encapsulation materials. Any matrices, fibers, granules or other materials that are used in addition to the cells can be categorized as fillers, additional active components or medical devices.

Both US and European legislation treat therapeutic products from human cells and tissues for transfusion or conventional transplants as biological products that retain their original characteristics when infused/transplanted into a recipient. Because it maintains original characteristics and functions, the conventional therapeutic use of cells and tissues does not provide proof of safety and efficacy by means of clinical trials approved by the health authority regulator, nor does it follow the same process of approval of marketing authorization of a classical synthetic or biological medicinal product. In this case, the requirements of Good Practices applied to the procurement and processing of cells and tissues are mandatory, in order to guarantee the quality of the biological material[10,12,13]. This same rationale is adopted by the Brazilian regulatory model for blood components, other tissues, cells and organs for purposes of conventional therapeutic use.

Advanced therapy products, which normally undergo significant manipulation and/or perform in the recipient a distinct function from that performed in the donor, need to be proven and reliable through clinical trials evaluated and approved by the regulatory body. They must also have marketing authorization so that they can be provided for therapeutic use. The Good Practice requirements also apply to advanced therapy products. A report by the European Medicines Agency (EMA)[16] about the regulation of ATMP recommended the rationalization of certification and registration practices for the marketing of advanced therapy products through the use of contact-promotion tools between the regulatory agent and the product developer center and its researchers, in order to create a favorable regulatory environment.

Risks in production vs. Good Manufacturing Practices

The WHO has defined Good Manufacturing Practices (GMP) as "part of the quality assurance that ensures that products are consistently produced and controlled, with quality standards suited to the intended uses"[17]. GMP covers all aspects of production, including validation of critical stages, adequate facilities, storage, transportation, qualified personnel, adoption of written and approved procedures, documentary records, traceability mechanisms, post-distribution non-conformities and complaints, among other aspects. For any products of human use it is essential to apply high standards of quality, production management and risk management system[18,19].

For ATMP, due to their complexity and the potential risks involved in their collection and manufacturing, the papers analyzed discuss the need to prove that extensive manipulation does not interfere with cell viability and does not generate sites of chromosomal instability. They also point out the importance of ensuring that

such a product acts safely and effectively on the pharmacological target site[19]. Some of the challenges lie in the variability and complexity inherent in the components used to generate the end product, such as the variable source of cells, the potential for contamination from donor and infectious agents, the production process and cell expansion with use of solutions, media and supplements, occasional processing in non-isolated environments, the inability to sterilize the final product, among others. According to D'Ippolito et al.[20], factors such as cell density, culture time, number of passages, temperature fluctuations, changes in pH and oxygen tension should be part of the control elements. Furthermore, the cultivation process in open systems, even if conducted under strict GMP requirements, can be affected by frequent changes in environmental parameters like temperature, PCO^2, PO^2, pH and humidity.

According to Herberts et al.[21], patients treated with these cellular products face risks of exposure to prions when using animal supplements, toxicological risks due to the presence of toxic agents like endotoxins and immunological risks due to the presence of proteins, peptides or other allogeneic biomolecules or due to the contamination of agents of animal origin that could persist after production. Distribution can also be a major challenge due to the instability of cellular products.

Advanced therapy medicinal products often constitute intricate solutions containing cells or their derivatives that cannot be chemically defined. This is what distinguishes them from classical biological medicines. The performance of quality control of the production process and of the final product obtained is considered essential. Improper production process controls may result in the introduction of contaminants and cause unknown changes in biological properties or product instability that may be undetectable in the final product approval trials. Another control factor is batch-to-batch reproducibility of both the final product and the critical materials involved in the production[22].

The scientific complexity related to advanced therapy products may impose practical limits on control processes. Concepts such as "batch", "dose" and "concentration" are diversified and peculiar, with highlights to the inability to control factors such as subject variability (donors). Furthermore, the documents analyzed pointed out that some products may take several weeks or months to be produced and that issues like cell viability and biological potency may decrease or change rapidly after the formulation. Therefore, "fresh" cells, which are not cryopreserved, may require administration within a few hours of production. Various authors also demonstrated risks in the cryopreservation and storage process[23,24,25].

In view of the risks identified, various authors stated that the establishment of Good Practices is intended to maintain these risks at an acceptable level of control, according to standards previously established by the cell processing center, minimizing the occurrence of exogenous contamination of the product and deterministically ensuring the quality and safety of the product in terms of infectious, immunological and toxicological risks[21]. In parallel with microbiological tests, endotoxin and pyrogen tests, quality control should include dose, viability and cellular functionality assessment, which would be directly related to the prognosis after use of the products. Keating[26] inferred that phenotypes should also be investigated, although the author describes the lack of standardized assays for certain cell types. In addition to the cell characterization methods, other advanced molecular tools, including evaluations of the cellular transcriptome, proteome and secretome should be understood[26,27]. It was suggested to evaluate the genetic stability of the cellular product, according to Barkholt et al.[28], even though there is still no definitive correlation with tumorigenicity. Both Barkholt et al.[28] and Wang et al.[29] reported conventional karyotyping as a low sensitivity test because it does not predict complete genome stability and suggested the adoption of high performance tests such as comparative genomic hybridization. After identifying the most appropriate control measures in each case, the producer should consider all potential risks related to the product, the manufacturing process and the use, based on the information available.

For these reasons, the analyzed documents pointed out the importance of the cellular processing centers – suppliers of advanced therapy products – implementing the quality management of their processes as well as being subject to evaluation of their production process by the competent authority conditioned to the inspection, as a way to ensure compliance with current regulations.

Risks of efficacy and safety vs. clinical trials

The papers argued that, in contrast to some classes of well-studied drugs, for example, biological products consisting of chemically defined molecules, there is a relative lack of clinical experience with ATMP. These products have unique complexity due to the dynamic nature of the cells. For example, cells can display a variety of molecules on their membranes and express various factors[19,30].

The development of a medicinal product should typically comply with the three traditional phases of clinical trials, starting with small-scale trials and testing a series of doses in healthy volunteers to establish the most tolerable dose (Phase I and Phase II) and, finally, clinical trials with a larger number of participants, designed to fully confirm and characterize the efficacy of the product (Phase III). Phase III trials provide a basis for cost-effectiveness analysis and subsequent marketing authorization. ATMP would not fit precisely in this framework. Because, for example, of the possibility of persistence of these products in the body after their application and possible related toxicity, the risk of using healthy individuals in Phase I becomes unjustifiable[30]. Early phase clinical trials are therefore usually performed with patients resulting in studies classified as Phase I/II. The diversity of advanced therapies requires a diverse approach, involving researchers, producers and regulators to approve the developmental logic and validation of the clinical trial project[19].

The systemic availability of products and the variety of tissues in the body could facilitate cell migration to unintended sites. It is even argued that the cells have the ability to differentiate *in vivo* into cell types or cell strains that are different from the infused originals and may develop undesired autonomic functions and

affect molecules and other factors according to the new microenvironment of insertion. The clinical appeal of most advanced therapy medicinal products is therefore based on their high proliferative and differentiating potential, especially in the ability to secrete cytokines, growth factors and other pharmaceutically and immunologically active substances[31,32]. However, these potentialities could also expose patients to oncogenic risk, as well as to the risk of ectopic differentiation[21]. Recent studies have reported indirect tumorigenesis related to the use of mesenchymal cells in animals[31,32,33].

Some products could persist in humans for a prolonged period after administration or have a prolonged or permanent effect, even after they are no longer present. Most of the application of the products requires surgery or other invasive procedures to access the target site. In addition, products of allogeneic origin have the potential to elicit immunological responses (immunogenicity). Induction of an immune response could be the desired effect of some products, such as therapeutic vaccines, however, for others, immunogenicity could be a risk[24].

Concerning data from preclinical to clinical studies, several problems could limit the ability, for example, to extrapolate safety information from a widely handled cell, depending on several factors, such as the animal models used, the product administration pathway, biodistribution profile, immune response to the administered product and others. Most regulatory agencies have discussed individualized clinical trial studies because of the particularities involved, especially when these products are intended for use in humans for the first time. In this case, the safety assessment must include the assessment of the nature and frequency of potential adverse reactions and an estimate of the relationship with the administered dose volume [34,35,36].

Chart. Description of the risks of the processes of production of advanced therapy medicinal products with mitigation strategies. Brazil, 2017.

Critical points	Risk Analysis	Mitigation
Raw materials	Microbial and viral contamination Variability of the final product	Degree of purity suitable for the intended use - pharmaceutical grade raw materials Traceability of raw materials Supplier qualification
Primary cells	Microbial and viral infection Material deterioration	Voluntary donation consent form Laboratory tests for the detection of infectious agents approved by the health authority Evaluation of the supplying collection centers Labeling and storage Traceability
Cell banks	Material deterioration Cross contamination	Labeling and storage Traceability Dedicated handling
Cultivation/Expansion	Microbial and viral contamination Genotypic alterations	Passage control in cultivation Laboratory control Validated processes Proper labeling and storage Inventory traceability
Processing	High variability Low reproducibility Product deterioration Microbial and viral contamination (no final sterilization)	Packaging and labeling Cryopreservation Quality controls with proper testing Production formula/Validated operating procedures Closed system production Sterile handling/clean environments Defined environmental controls Change control Deviation analysis and risk management Controlled batch release Maintenance of analytical sample of final product (if possible) Product stability studies
Infrastructure	Cross contamination Product deterioration Microbial and viral contamination Worker safety	Water treatment system Defined flows Segregated production Air treatment systems Validated sanitation/decontamination/sterilization or filtration processes Room for replicated materials/vectors and room for segregated infected products Qualified and controlled equipment (bioreactors, chromatographic columns, radiators, deep freezers, N2 tanks etc.) Formalized and audited outsourcing
Personnel	Absence of quality control of processes, final and batch release	Qualification and training
Recall	Use of inappropriate products Worsening patient health	Defined product recall procedures Procedures in cases of non-compliant products already used in patients
Waste	Contamination of the environment	Procedures for collection and treatment of waste Special attention to vectors (GMOs)

Cell processing is generally segmented into a series of steps defined according to the cell types and the specific needs of the product. A typical GMP process for advanced therapy products should follow the following steps[23,28]:

- Selection of donor cells or starting material with laboratory screening for markers of infections transmissible by biological material.
- Evaluation of the starting material (cells, tissues) obtained by donation, from a cell and tissue bank.
- Wash to remove unwanted/non-viable cells.
- Selection/enrichment of target cells.
- Cellular engineering – genetic modification, activation.
- Cell culture – static or bioreactor platforms.
- Wash to remove impurities.
- Product formulation – volume reduction and cryopreservation.
- Storage.
- Final transportation of the product and distribution to the health service for patient use.

In the case of gene therapy using vectors, vector amplification, cell transfection, transduction, population purification or distinction, microfiltration/ultrafiltration and transfer are added to the aforementioned steps[23,24].

The table describes the main critical points of the production of an advanced therapy product, considering the risks involved and the proposed mitigation of these risks, based on the GMP premises defined by Abou-El-Enein et al.[38] and referenced in a Public Consultation document on the same subject, published by the EMA in 2016[39].

Finally, the detailed description of the conditions of use of the advanced therapy product must be carefully elaborated and informed by the manufacturer of the product to the person in charge of the use/application of the product and must also include the specifications of the equipment and the characteristics of the manufacturing environments[37,39]. Risks related to improper handling, post-release of the product and prior to its use, have the potential to impair the quality and safety of the product as well as increase the risks associated with the production process. Among the possible minimal manufacturing situations required for pre-use, we have: thawing, washing, buffer replacement, centrifuging to remove preservation solution containing cryoprotective agent, removal of impurities related to the process (filtration to remove residues of solution of preservation or non-viable cells), suspension, dispersion, dissolution or dilution with solvent/buffer, recovery of cells after cryopreservation, mixing of the product with autologous cells or other adjuvant, sampling and dose adaptation, loading into surgical systems or devices or bag transfer of infusion/syringe[37], among others.

Therefore, the complexity inherent in the development of an advanced therapy product should reflect in product development plans meticulously adjusted to the multifactorial assessment of the risks inherent in the process, in order to identify factors associated with the impacts on product quality and safety, determine the extent and focus of the data required during the development of non-clinical and clinical studies and establish pre-market and post-market risk management processes to be specified in the pharmacovigilance plan[37]. It is important to consider that advanced therapies have, additionally, a certain ethical dimension that is not present in the traditional processes of pharmaceutical development. Therefore, the progression from preclinical trials to successful clinical trials, by the provision of approved products to the population, needs to be considered within the historical and ethical framework of the country[36].

CONCLUSIONS

The analysis of the scientific literature has demonstrated significant progress in human cell studies and their therapeutic potential, although there is still some uncertainty about the risks involved in the use of advanced therapy products in the long term. The low predictability of preclinical studies limits the availability of the respective products for use in humans. So far, the lack or shortage of harmonization of protocols related to cell or tissue procurement, methods of isolation, cell culture and expansion, characterization and quality controls of intermediates and final products has been detected. The FDA and the EMA have made successful efforts to establish rules for advanced therapy products that are compatible with GMP and conduct clinical trials. Likewise, the scientific community has been committed to developing advanced tools for cell studies in *in vitro* and *in vivo* models.

Some challenges described, like the intrinsic variability related to the source of the biological materials, make it difficult to demonstrate the homogeneity of the product, as well as condition the limited batch size and the short half-life time, somehow affecting relevant parameters such as in performing extensive control tests. Furthermore, conducting randomized controlled clinical trials may not always be feasible, for example, if the administration of the product requires an invasive and high-risk surgical procedure.

Another point is the difficulty in translating basic research procedures into large-scale production for human use, mainly due to the lack of expertise in regulatory processes. In this regard, it is possible to conclude that regulatory instruments should be optimized in order to be dynamic, since advanced therapies are a field of medicine subject to rapid scientific progress. Accordingly, regulatory agencies should review and rationalize the requirements for marketing records and product use authorizations to ensure that the applicable rules are proportionate and well-adapted to the specific characteristics of advanced therapy medicinal products.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.