22 The Regulatory Landscape of Cell- and Tissue-Based Regenerative Medicine: Current Challenges and Emerging Issues

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22.1 Introduction

Rather than managing sustained disease or damage, the field of Regenerative Medicine (RM) is aimed at restoring or establishing normal function by replacing or regenerating human cells, tissues, or organs [1]. As a subdivision of translational research in molecular and cell biology, biomaterial science, and organ and tissue engineering [2], RM holds great promise in addressing the global lack of organ supply, aging-related diseases, and congenital or acquired defects by either actively reconstructing de novo organs [1] and/or tissues or functionally healing previously irreparable tissues or organs by stimulating the body's own repair mechanisms [1].

Under this umbrella, researchers have been working vigorously on the development and bench to bedside translation of a variety of innovative therapeutic products such as: human cell and tissue products, tissue engineered therapeutic products, gene therapy products, and combined products. However, despite the continuous advances in science and technology paving the way in the development of Regenerative Medicine Therapeutics (RMT), to date, only few products have been authorized for marketing in the United States (US) and the European Union (EU).

To better understand how the EU and the US manage the development and manufacture of RM products, details regarding the regulatory process from the first step of classification until market approval will be addressed here.

22.2 EU and US: Different Approaches When it Comes to Medicinal Products

In the EU, the evaluation and regulation of the translation and marketing of RMTs is overseen by the European Medicines Agency (EMA).

The original version of this chapter was revised. The correction to this chapter can be found at https://doi.org/10.1007/978-3-030-19958-6_36

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D. Duscher, M. A. Shiffman (eds.), *Regenerative Medicine and Plastic Surgery*,
https://doi.org/10.1007/978-3-030-19958-6_22

RMTs that are designated as Advanced Therapy Medicinal Products (ATMPs) are pharmaceuticals with a high level of complexity linked to their composition, development, manufacturing, characterization and administration, and represent the forefront of medical research, blurring the lines between medicinal products and medical devices. They are comprised of somatic cell therapy medicinal products, tissue engineered products, gene therapy medicinal products or combined ATMPs (Fig. 22.1). They are derived from living human tissue, which is then manipulated in such a way that it can then be used in a therapeutic setting [3–6].

Somatic cell therapy medicinal products (SCMPs) consist of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions, or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor. SCMPs are presented as having properties for, or are used in or administered to human beings with a view to treating, preventing, or diagnosing a disease through the pharmacological, immunological, or metabolic action of its cells or tissues [7].

Tissue engineered products (TEPs) consist of engineered cells or tissues, and are presented as having properties for, or are used in or administered to human beings with a view to regenerating, repairing, or replacing a human tissue. TEPs may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. They may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds, or matrices [3].

Gene therapy medicinal products (GTMPs) either contain an active substance that consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding, or deleting a genetic sequence. Its therapeutic, prophylactic, or diagnostic effects relate directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence. GTMPs do not include vaccines against infectious diseases [7].

Combined ATMPs contain one or more medical devices as an integral part of the medicine, such as cells embedded in a biodegradable matrix

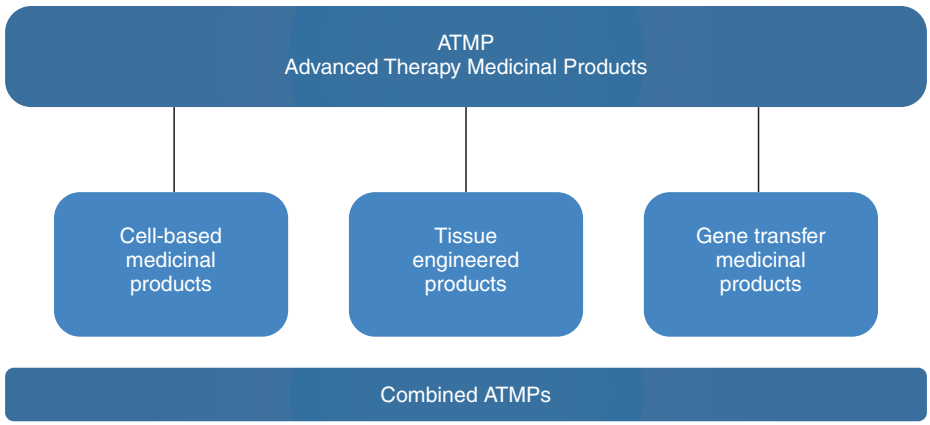

Fig. 22.1 Classification of ATMPs according to EMA. (Adapted from Paul-Ehrlich-Institut Booklet [8])

or scaffold [3]. The translation of different ATMPs into the market requires the obtainment of a marketing authorization (MA). When attempting to translate an ATMP into the market, it is important to note that it is essential to comply with ATMP regulations, as well as EMA's regulatory system.

In the United States, the body responsible for the evaluation and regulation of the translation and marketing of RMT products is the US Food and Drug Administration (FDA). The FDA regulates most RM products under the Food and Drug Safety Act, Title 42, Chapter 6A- Public Health service, Public Health Service Act Section 361 and 351 (PHS Act 361, Title 42 USC Section 264) and Code of Federal Regulations Title 21 Part 1271 (21 CFR 1271) in a risk-based tiered structure [9]. RM products are regulated as human cells, tissues, and cellular and tissue-based products (HCT/Ps) based on the criteria defined in 21 CFR 1271.10 (a) [10], and are defined as "Human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient" (21 CFR 1271.3(d)(1) and Section 361 of the PHS Act). If they meet all of the criteria, they are regulated by the Center for Biologics Evaluation and Research (CBER) solely as 361 products do not require additional regulatory oversight (not subject to pre-market requirements) and follow the 'tissue rules' [11]. Examples of products regulated solely as 361 products include: skin, Dura mater, bone (including demineralized bone), and cartilage [11, 12]. RM products that do not fulfill one or all of the criteria can be regulated as:

1. Drugs and/or Biological Products, such as human somatic cell therapy and gene therapy products (which are also regulated by CBER under Section 351 of the PHS Act and/or the FD&C Act) and require additional regulatory oversight (pre-marketing requirements) [11, 12]. Examples of products falling under this designation include: lymphocyte immune therapy products, gene therapy products, and cultured cartilage cells.
2. Medicinal Devices composed of human tissues (regulated by the Center for Devices and Radiological Health (CDRH), under the FD&C Act and device regulations) and also require additional regulatory oversight (such as preserved umbilical cord vein grafts and human collagen) [11, 12].
3. Combination Products, which combine more than one type of product, are regulated based on the mode of action of the product. Requests for Designations (RFDs) of combination products are handled by the Office of Combination Products (OCP) that determine the responsible office within the FDA [13]. Examples of Combination Products include: encapsulated pancreatic islet cells (regulated as biological products), bone-suture-tendon allografts (regulated as devices), and demineralized bone combined with handling agents (e.g., glycerol or sodium hyaluronate) (regulated as devices) [11, 12].

Most advanced therapy products are regulated as Drugs and/or Biological Products. Recognizing the importance of the regenerative medicine field, and to facilitate the development and approval of RM products, a new program has been established that allows applicants with RM products to file for approval with a Regenerative Medicine Advanced Therapy (RMAT) Designation [14]. Drugs are eligible for RMAT designation (Section 3033 of the Twenty-first Century Cures Act) if:

1. the drug is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations;
2. the drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition;
3. preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition [15].

Applicants filing for an RMAT designation must do so in addition to filing an Investigational New Drug application (IND) or as an adjustment to an already existing one [15].

Therefore, addressing regulatory issues concerning cell- and/or tissue-based regenerative medicine products to further develop them into the clinic, begins with the accurate definition and classification of the intended product. It is important to notice that to develop/manufacture a product, the product must be, first, accurately defined and subsequently regulated.

22.3 Classification of RM Products in the EU and the USA

Both EMA and FDA officially classify products when reviewing market or pre-market submissions. However, to select the accurate regulatory submission path and to fully comprehend the extent of regulatory control required to ensure the safety and effectiveness of the product, it is important for manufacturers or stakeholders to identify the classification beforehand [13].

Similarities exist between the EU and the US in the classification of RM or cell- and tissue-based products, mostly about the considerations of: major vs. minor manipulation [16], intended use for its original function, and risk assessment in the classification of the products. However, here is where the similarities end, and this is largely due to the approach in the designation of the products.

In the European Union (EU), cell/ tissue-based products are regulated as ATMP medicines for human use (Article 17 of Regulation (EC) No 1394/2007) (and classified accordingly) [17] when they have been substantially manipulated and/or are not intended to be used for the same essential functions in the recipient as in the donor (not for homologous use). Non-substantially manipulated cells or tissues used for the same essential function are not considered ATMPs.

Minimally manipulated cells and tissues that are not considered medicinal products are regulated under EUCTD (2004/23/EC): donation, testing, procurement, processing, storage, and distribution across the EU. Example: preparation of enriched populations based on immunophenotypic markers such as CD34 or CD133 for haematopoietic transplantation. Examples of procedures that are considered to be of minimal (non-substantial) manipulation include: cryopreservation, cutting, filtering, cell separation, concentration or purification, irradiation, and filtering (i.e., they do not alter the biological characteristics or structural properties relevant for the intended function) [17]. However, in Germany, the Transfusion Act (TFG) defines blood cells and cell preparations from peripheral blood as medicinal products.

Substantially manipulated cells/ not the same essential function(s) are covered by the Regulation 1394/2007/EC and are classified as Advanced Therapy Medicinal Products (ATMPs), which include three categories: (a) somatic cell therapy medicinal products as defined in Part IV of Annex I to Directive 2001/83/EC; (b) gene therapy products as defined in Part IV of Annex I to Directive 2001/83/EC; (c) tissue engineered products as defined in Article 2(1) (b) of Regulation (EC) No. 1394/2007; (d) combined ATMP products under Article (2) (1) (d) of Regulation (EC) No. 1394/2007 [18].

Products in the EU can also be classified according to risk. Cell-based products are considered to be of high risk if the product has been: (a) subjected to a substantial amount of manipulation; (b) used for a function(s) different from its original function); and (c) if the product is combined with another product. All xenogeneic cell-based products are classified as ATMPs by default.

In the US, however, classification, and thus designation of products, is much more complex. RM products can be:

1. HCT/Ps and given the 361 designation are of low risk if they meet all of the criteria under 21 CFR 1271.10(a): (a) it is minimally manipulated; (b) it is intended for homologous use only; (c) it is not combined with another article; and (d) it does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or, it has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and is for autologous use, for

allogeneic use in a first or second degree blood relative, or for reproductive use [10]. These products are not subject to pre-marketing requirements [19].
2. HCT/Ps that do not meet one or more of that criteria can be classified as either drugs, biologics, and/ or devices under Section 351 of the PHS Act and/or under the Food Drug and Cosmetics Act. These products are of high risk and are subject to pre-marketing requirements [19].
3. Products that contain one or more combination products (as defined in 21 CFR § 3.2(e): products comprised of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product) are classified as combination products and based in their classification on their primary mode of action for their primary designation.

On substantially (major) manipulated vs. non-substantially (minimally) manipulated products, generally, both the US and the EU have similar definitions as to what constitutes major/substantial manipulation and/or minor/or non-substantial manipulation. In the EU, substantially manipulated products encompass manipulation throughout the manufacturing process so that the physiological functions, biological characteristics, and/or structural properties of cells and/or tissue(s) have been relevantly modified for their intended function [17]. Some examples include: the enzymatic digestion of tissues and cells that have been artificially expanded in culture, treated with growth factors for differentiation/activation, and/or cells that have been genetically modified. In the US, the FDA substantially manipulated is classified under Title 21 of the Code of Federal Regulations (CFR) Part 1271, specifically 21 CFR 1271.3 (f). Minimally manipulated products are defined as "products that if containing structural tissue, have been processed in a way that does not alter original relevant tissue characteristics related to the tissue's utility for reconstruction, repair, or replacement; and if containing cells or non-structural tissues, have been processed in a way that does not alter relevant biological characteristics of the cells or tissues" [20].

22.3.1 Intended Use or Essential Function (Homologous or Non-Homologous Use)

If no substantial manipulation takes place, products are classified according to the essential function of the cells/tissues. Products are considered of homologous use when the "repair, construction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor" [20] (under the US FDA's regulation Title 21 of the Code of Federal Regulations (CFR) Part 1271, specifically 21 CFR 1271.3(a) (2)/1271.3 (c) criterion and definition of homologous use) [10]; or, "when removed from their original environment in the human body are used to maintain the original function(s) in the same anatomical or histological environment" [17]. An example of homologous use would be donated bone marrow for leukemic patients that have undergone total body irradiation (TBI) [17].

22.3.2 The Product's Claimed Mode of Action (MoA)

The product's claimed mode of action answers questions on whether the product is meant for diagnosis, prevention, or treatment of disease. Does it exert its activity via a pharmacological, immunological, or metabolic action? Alternatively, is the product intended for regeneration, repair, or replacement of cells/tissues? [17].

22.3.3 Other Points Taken Into Consideration When Classifying a Product

1. Their status as living sources: the biologics of the medicinal products for human use [21].
2. The origin of the cells utilized (cell source): autologous or allogenic [16, 21].
3. The application of the anatomical/histological environment [9].

22.4 The EU Legal Framework for ATMPs

A consolidated regulatory framework for the development of ATMPs in Europe came into force in 2008 [22]. The overall framework on ATMPs is provided by Regulation (EC) No 1394/2007, which amended the Medicines Directive 2001/83/EC, and established the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA). The EMA is a decentralized agency of the European Union (EU) responsible for the scientific evaluation, supervision, and safety monitoring of medicines in the EU, and the CAT is a multidisciplinary committee, whose primary responsibility is to assess the quality, safety, and efficacy of ATMPs, and to stay up-to-date on the developments in the field. When it comes to regenerative medicine products, the Committee for Medicinal Products for Human Use (CHMP) under the EMA is in charge of evaluation and approval. All legislatures relating to medicinal products, including regenerative medicine products, are data based in the EudraLex. This regulatory framework is designed to ensure the free movement of these medicines within the EU, to facilitate their access to the EU market, and to foster the competitiveness of European pharmaceutical companies in the field, while guaranteeing the highest level of health protection for patients [23].

As this regulatory framework for ATMPs in the EU, because of constant advances in the field of regenerative medicine, is dynamic, complex, and advances rapidly, early interactions with regulatory agencies to ensure collaborative discussions between clinical product developers and regulatory experts are a 'must'. Hence, many regulatory agencies globally encourage and provide opportunities, such as a Scientific Advice Meeting with a national competent authority (e.g., Paul-Ehrlich-Institute, Germany) and/or EMA [6].

The CAT issues scientific recommendations on ATMPs under the ATMP Regulation (Article 17) [17]. Its recommendations are based on definitions laid down in the EU legislative texts:

1. Regulation (EC) No. 1394/2007 on ATMPs provides the definitions of "tissue-engineering product" and combined 'ATMP'.
2. Part IV of Annex I to Directive 2001/83/EC provides the definitions of "gene-therapy medicinal product" and "somatic cell-therapy medicinal product" [17].

At the inception of the development of a product, it is important to consider seeking CAT classification, which is an optional, no-fee procedure. However, achievement of such status holds significant merit in obtaining fee reductions for EMA scientific advice and potential benefits in successfully navigating the clinical trial application process through national authorities in Europe [24].

Developers of ATMPs should also consider if their product may be eligible for the newly introduced Priority Medicines (PRIME), which is a voluntary scheme launched by EMA in 2016 to enhance support for the development of medicines targeting an unmet medical need [6].

In addition to the existing complexity, in Europe certain ATMPs are also considered a Genetically Modified Organism (GMO), i.e., an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination (Directive 2001/18/EC). In the EU, before a clinical trial can commence for ATMPs considered GMOs, besides the ethics committee and competent authority approval, a GMO approval must also be obtained. Nevertheless, the regulatory classification processes and requirements for GMO approval are not sufficiently harmonized between the EU Member States, despite the EU Deliberate Release (2001/18/EC) and the Contained Use (2009/41/EC) Directives, resulting in significant challenges and timeline considerations [6].

The process of ATMP market approval starts with the collection of tissues and cells from donors and their evaluation under the European Union Tissue and Cells Directives (EUTCD), the

EU version of Good Tissue Practice (GTP). Preclinical testing for safety of the product will be performed under Good Laboratory Practice (GLP), similar to the USA [25].

On scientific and technical aspects of drug registration, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), as a tripartite initiative between Europe, the US, and Japan, takes place bringing together the regulatory authorities and pharmaceutical industry [26]. To bring new medical product to market, clinical trials are required by regulatory authorities of the originating countries [26]. When the product is adequate for market approval, it will lastly be evaluated by the EMA as a final step to market application. ATMPs will be required to obtain continuous post-market evaluation on the traceability of the donors, products, and patients, as well as the development of risk management systems and pharmacovigilance, especially for follow-up on efficacy and safety. Similar to the situation in the USA, the whole process may take multiple years (Fig. 22.2) [25].

Although the ATMP regulation has been in place for more than 10 years, the number of marketing authorization applications and successful approvals in the EU remains in single figures. Of the 18 marketing authorization applications submitted to EMA since the ATMP regulation came into force in 2009, EMA said nine products have been approved [27]. However, of those nine approved, four have been withdrawn from the market or suspended. For instance, UniQure's Glybera, the first gene therapy authorized in Europe in 2012, was later withdrawn from the market. Similarly, Dendreon's Provenge and TiGenix's tissue-engineered product ChondroCelect, approved in 2009, were also withdrawn. Vericel Denmark's Maci in 2013 was suspended at the recommendation of the Committee for Medicinal Products for Human Use (CHMP)[27].

Other ATMPs remain on the market and include German company CO.DON AG's Spherox, approved in 2017, MolMed S.p.A.'s Zalmoxis, approved in 2016, as well as Chiesi Farmaceutici's Holoclar, GlaxoSmithKline's Strimvelis, and Amgen's Imlygic [27].

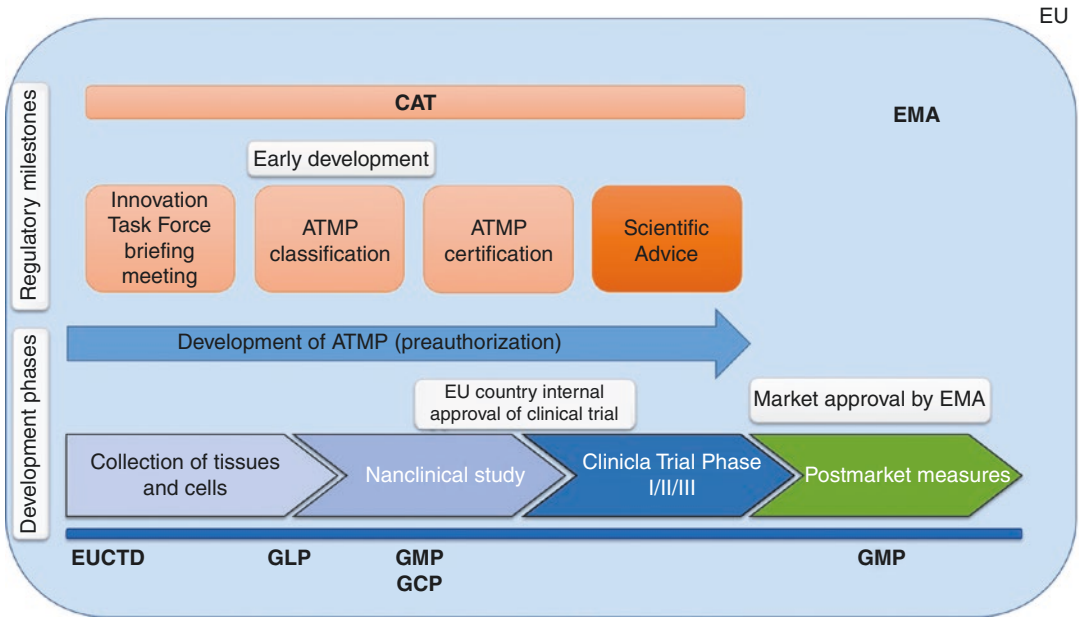

Fig. 22.2 Regulatory pathways and development phases for ATMPs in Europe. (Adapted from Sakai et al., 2017 [23] and Maciulaitis et al., 2012 [25])

22.5 The US Legal Framework

In the ensuing successful pre-clinical investigations (laboratory and animal testing to answer basic questions about safety, devoid of human participants, and mainly conducted under Good Laboratory Practices (GLP) conditions) (21 CFR Part 58) [28–30], with the aim of translation of RM products into the market, sponsors/stakeholders must follow a series of steps under the governance of FDA regulatory requirements (Fig. 22.3) [23].

To select the accurate regulatory pathway and identify its requirements, sponsors/stakeholders must first accurately classify their products. The FDA officially classifies products during the review of the pre-market submission. However, it is the responsibility of the applicant to ensure the correct classification of the product that has been applied [13]. FDA regulation focuses on the:

1. Prevention of inadvertent transmission of infectious diseases such as AIDS and Hepatitis through the use of contaminated tissues.
2. Prevention of contamination and/or damage through improper handling and/or processing.
3. Ensuring that clinical safety and effectiveness is demonstrated, in a risk-based tiered approach [21, 31].

HCT/Ps that meet the requirements (criteria under 21 CFR Part 1271.10(a)):

1. are considered of low risk [19];
2. are regulated under the 361 route;
3. do not need to apply for pre-market approval; and
4. only need to meet the "tissue rules" requirements (21 CFR Part 12714) [11].

HCT/Ps that are more than minimally manipulated, are of non-homologous use, are not combined with other articles (except for water, crystalloids, or sterilizing preserving, or storage agent), do not have a systemic effect and/or are not dependent on the metabolic activity of living cells for their primary function (if they have such an effect, they are intended for autologous use or allogeneic use in close relatives or for reproductive use) (criteria under 21 CFR Part 1271.10(a)), and/or do not qualify for exemptions under 21 CFR 1271.15 [32], are of high risk [19]:

1. are subjected to pre-market review requirements and approval; and
2. are regulated as drugs, devices and/or biological products under 351 of the Public Health Service Act (PHS).

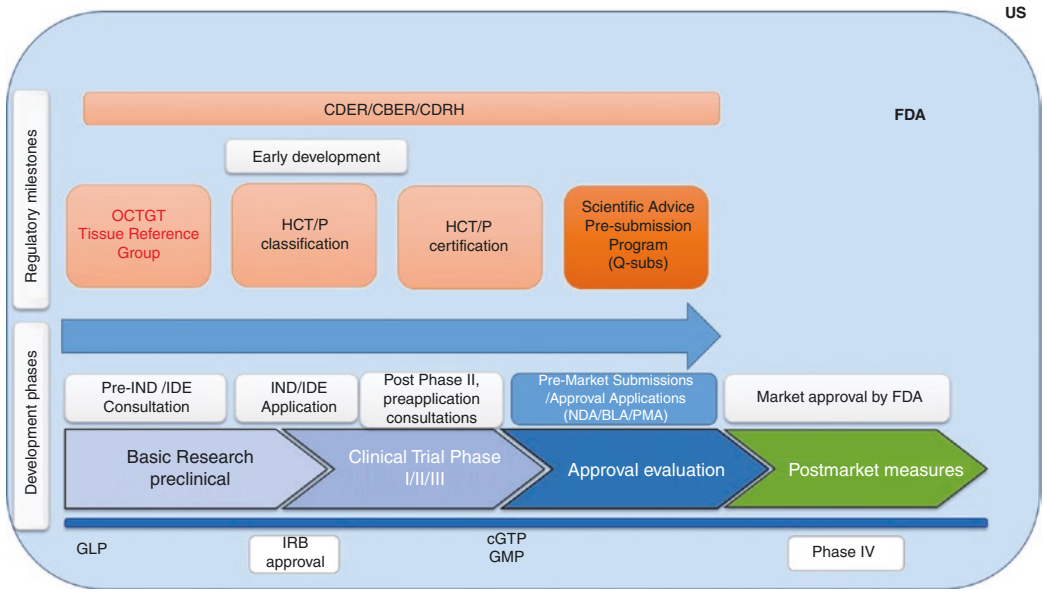

Fig. 22.3 Regulatory pathways and development phases for RM products in the USA. (Adapted from Sakai et al., 2017 [23] and FDA Regulations). CDER: Center for Drug Evaluation and Research, CBER: Center for Biologics Evaluation and Research, CDRH: Center for Devices and Radiological Health, IND: Investigative New Drug, IDE: Investigational Device Exemption, NDA: New Drug Application, BLA: Biologics Licence Application, PMA: Premarket Authorization, OCTGT: Office of Cellular, Tissue and Gene Therapies classification

Examples of products that are regulated as drugs and/or biological products include: gene therapy products, cultured cartilage cells, and unrelated allogeneic hematopoietic cells. Tissue engineered products, however, are more often than not considered to be combination products containing scaffolds, cells, and drugs. Thus, they are regulated according to their primary mode of action (or intended therapeutic effect to be either drugs, devices, and/or biologics) to be determined by the OCP (Office of Combination Products) and forwarded to the relevant centers to lead the review on the product [13].

Pre-market approval applications vary according to the classification of the product. Once the correct classification of a product has been identified, clinical trials can commence under exemption from FD&C Act for new drugs and devices, and PHS ACT for biologics laws, by submitting the applications. Examples of different pre-market approval applications include: Investigational New Drug (IND) (21 CFR 312) for drug or biologics introduction (very common with ATs) or an Investigational Device Exemption (IDE) (21 CFR 812) for device introduction [33]. Applications such as INDs comprise information on the product, data on toxicity and animal studies (possible detrimental side effects), information on the manufacturing process, the planned clinical protocols, data on any prior research on humans, and investigator's information [33, 34]. The FDA also provides pre-investigational new drug (pre-IND) consultation services for researchers and manufacturers and to optimize the IND submission process; after which, formal pre-IND meetings with the Office of Cellular, Tissue, and Gene Therapies (OCTGT) are conducted [35].

Before the commencement of clinical trials, however, the Institutional Review Board (IRB) (21 CFR56) that is responsible for governing the rights of human participants in research programs [33, 36, 37] must review all information related to the IND/IDE application such as: verification of the IND/IDE approval, qualifications of the clinical investigators, suitability of the research site, approval of the Standard Operating Procedures (SOPs), compliance with Good Clinical Practices (GCPs), risk assessment determination, and subsequently, grant approval [33, 36]. Risk assessment determination for the classification of medical devices is initially conducted by the sponsor/stakeholder, and is determined according to the degree of risk a medical device poses according to the following [13, 33]:

- Class I- Low risk products/devices that are subjected to general controls.
- Class II- Moderate Risk products/devices that are subjected general controls and special controls.
- Class III- High risk products/devices that are subjected to general controls and pre-market approval.

Class III- significant risk (SR) designations require an IDE submission and approval, and an IRB approval before clinical investigations [13, 33]. Non-significant risk (NSR) designations do not require IDE submissions [33]. After the submission and approval of the pre-marketing applications, clinical trials can commence.

IND pre-marketing applications for drugs and biologics require three phase clinical trials, and a fourth phase post market approval.

Before applying for final approval, FDA consultations can be held after Phases II and III [23]. With Medical Devices however, single confirmatory feasibility studies conducted under IDE applications that allow for early clinical evaluation of devices to provide proof of principle and initial clinical safety data (with a small number of subjects, first human (FIH) studies), can be sufficient for FDA approval [33].

Post successful Phase III clinical trials, pre-marketing submissions must be handed in to the FDA before marketing [19]. The pre-submissions program allows sponsors or stakeholders to consult the FDA during submission preparations for early feedback before the pre-market submissions in the form of 'Q submissions' or 'Q-subs' [33]. Examples of pre-market submissions include: PMA- Premarket Approval (Class III) submissions and De Novo- new device submissions for Class III medical devices, BLA- biologics license application for biologics [19], and NDA- New Drug Application for drugs [13, 33]. After receiving positive feedback from the FDA, formal applications are submitted.

Following positive review and subsequent approval for marketing, the sponsor/stakeholder can then market the product and post marketing Phase IV data is collected. Recently, the FDA created a new expedited designation for the RM products termed the Regenerative Medicine Advanced Therapy (RMAT) Designation that can be filed with or post IND application [15].

Some of the cell therapy products that have gave gained licensing in the US as biologics include: autologous cultured chondrocytes (Carticel®), autologous cellular immunotherapy (Provenge®), autologous cultured fibroblasts (Laviv®), and hematopoietic progenitor cells, cord blood (HEMACORD®) [23].

22.6 Hurdles in the Development of RM Products

Despite many advances made in science and technology, and large progression in various aspects of the RM field development, many hurdles prohibiting the mainstreaming of such products within a single jurisdiction and on an international scale exist as regards to:

22.6.1 Regulation

A large barrier preventing the mainstreaming and standardization of RM products on a global scale is Regulation. Regulatory barriers can generally be summed up into two themes:

22.6.1.1 Regulatory Clarity

Different countries define RM or Human Cell and Tissue (HCT) products in different contexts [19]. Since accurate product definitions leads to accurate classification, and subsequent application of the correct regulatory requirements, variations in definitions between different jurisdictions create quite a challenge for sponsors/stakeholders aiming to manufacture and/or distribute products in multiple countries, and results in the disruption of a global harmonized development of RM products [16].

In addition, some products that are termed 'borderline products' and defined as "products that might fall between two or more regulated product categories" (ATMPs or blood products and cell transplants) are very difficult to define, and highlight the vague line between what is considered an ATMP and what is not, with important consequence on the developmental pathway the product will take (e.g., lymphocyte immunotherapy) [9].

22.6.1.2 Regulatory Framework and Jurisdiction

The jurisdiction of different regional guidelines vary immensely on product type [16]. For manufacturer/developer to identify product specific requirements, unification and standardization of requirements of is of paramount importance. Thus, variations in guidelines pose a hurdle for global development [16].

22.6.2 Translation: Academia and Industry

Another barrier is the translation of innovative therapeutic science from its source. Academic institutions are vibrant sources for the generation of science leading to novel therapeutics. However, they often face hurdles in the form of lack of regulatory expertise. In academia, the development of RM products is usually science driven rather than product-driven [38]. This generally results in a lack of understanding for basic regulatory requirements of the translation of a product into the market, and a subsequent failure in that regard [16]. In addition, when it comes to funding, it has been observed that for many RM products, especially cell-based and patient-specific treatments, the pharmaceutical industry has limited interest in playing its 'usual' role of financing development and acting as a sponsor in clinical trials. The relative dearth of industrial investment in the RM products lies behind several aspects, including: distribution, economic, as well as cultural issues [39, 40].

22.6.2.1 Distribution Models

Depending on the type of product, decentralization of ATMP manufacturing might be needed,

and to achieve that, it is imperative that the origin, composition, manufacturing process, quality control methods, as well as batch release specifications are aligned between both the regulatory agencies and the ATMP manufacturers. Products that might require a decentralized distribution model are cell-based therapies. When compared to other biologicals they have a shorter shelf life and, therefore, are particularly susceptible to damage during shipping, which influence the final quality of these products. One such example is Holoclar, where patient biopsies must be received by the manufacturer within 24 h following procurement and which has only a 36-h shelf life. Due to the temperamental nature of such products, one suggestion has been the establishment of regional sites or centers of excellence, which could offer a more suitable model for personalized autologous cell products or for rare diseases. Of course, consistency of approach and the necessary standards and guidelines would have to be conserved across these different regional sites and agreed on by the necessary regulatory authorities [40].

Nevertheless, in 2017, using a centralized model, big pharmaceutical companies managed to receive marketing approvals of three gene therapy products: Kymriah, Yescarta, and Luxturna [41, 42].

Economic

1. Intellectual Property. Since ATMP are often not based on a 'simple' cause-effect model, the intellectual property landscape is often more complicated with these products, making it difficult to ring-fence intellectual property, establish freedom to operate, and anticipate the effects of competition [39].
2. Orphan. Many current ATMPs, especially in gene therapy, are applicable for rare or orphan indications. While it is now established that orphan drug status in itself is no bar to profitability, the challenges with developing and finding politically acceptable reimbursement for such products remain [43].
3. Scalability. Even if ATMPs are potentially applicable to a large patient population, their cost and complexity often render it impossible to conduct trials on a large patient population—which is traditionally the specialist expertise that industry brings to the table in translational research. The high cost effort per treatment also yields uncertainties about effective reimbursement [44].
4. Costs. Translational costs related to all aspects of GMP manufacturing, from GMP-grade stating materials to the personnel required to run such facilities, poses a huge burden on the sponsors/stakeholders aiming to market a product [4].

Cultural

1. Complexity. Many ATMPs are manufactured differently from mainstream medicines, requiring investment into new expertise. Cell therapy products often do not have a clearly defined mechanism of action, gene therapy presents unique challenges of long-term systemic effects, and tissue engineering targets a complex interface of material science and biology. The selection, enrichment, or genetic modification of cells and tissues often enhances their sensitivity the effect of which cannot be replicated in vitro [39].
2. Surgical. Many ATMPs are seen to be more closely related to transplantation, an area that does not interface much with established industrial R&D [39].
3. Transferability. Many ATMPs require very specialized, tacit clinical expertise that cannot easily be transferred. Cell populations are necessarily heterogeneous and dynamic, and purification protocols, as they are applied in 'established' biotechnology may actually prove detrimental to the efficacy of the final product [39].

Ethics

A third hurdle that faces RM streamlining surrounds ethical considerations and difference in belief. Ethical hurdles exist on cell sources and ownership, such as: the utilization of embryonic stem cells and/or fetal tissue, which may be allowed in some countries and prohibited in others. In addition to this, controversies exist over whether human cells/tissues can be subjected to

laws regarding property rights [33]. Ethical objections to the implementation of certain procedures such as: therapeutic cloning of cells, genetic engineering of cells, and the mixing of human and animal cells on the production of RM products have been raised [33]. Moreover, a 2008 study indicated that physicians have less confidence in industry-funded clinical trials as opposed to government-sponsored trials [33].

These issues and challenges are not meant to suggest that ATMPs are not attractive for industrial development. Other factors play a role [45] and in fact, the industry sector using ATMP is increasing markedly [46]. However, the above considerations suggest that there are a number of factors that may militate against ATMP development in the private sector and complicate technology transfer from the public sector [39].

22.7 Overcoming Hurdles: the Formation of Collaborative Parties

To overcome challenges resulting from diverse regulatory pathways associated with different countries, and to facilitate the acquisition of marketing approval under multiple jurisdictions, several international collaborations have been established. To that effect, information on science and regulatory convergence related to ATMPs or HCT/Ps manufacturing, and the marketing of products, in several countries can be gained from different alliances groups such as: the EMA-US FDA Parallel Scientific Advice (PSA) [47] (during which each regulatory agency (EMA and FDA) provides the sponsor/ stakeholder with independent advice regarding questions presented) and the Life Sciences Innovation Forum (LISF) (under Asia-Pacific Economic Cooperation (APEC)) both provide meaningful dialogue with stakeholders regarding successful implementation of policies.

Other collaborative clusters that work towards the harmonization of ATMP production include: the US FDA-EMA-Health Canada Advanced Therapy Medicinal Products Cluster [47] and the Regulators Forum (RF): composed of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) members, the ICH observers, regional harmonization initiatives, and different drug regulatory authorities from various countries (e.g., Brazil and Australia) [47].

On different industries (education, pharma, health care, and regulatory), academic initiatives such as the EuroTech Universities Alliance [48] have been established, and work towards facilitating translation of basic science and technology into the clinic. Groups such as the ATMP Interest Group, founded in 2017 by the European Compliance Academy (ECA), have representatives from the academia, industry, and the regulatory authorities, and aspire to facilitate information exchange between academia, pharma, and regulatory bodies on Good Manufacturing Practice (GMP) and pharmaceutical quality assurance. The ATMP Interest Group in collaboration with the ATMP GMP Open Access Research Alliance (AGORA) group work on the AGORA project [49], which has contributed to the much needed support and training framework for the facilitation of regenerative medicines implementation by establishing a technology transfer network, training programs, and interactive information sources [48].

Other structures, such as the European Society for Blood and Marrow Transplantation (EBMT) [50], have been developed beyond bone marrow transplantation towards modern cell therapies to allow scientists and physicians to share experience and develop cooperative studies. The EBMT together with the International Society for Cellular Therapy (ISCT) have formed the Joint Accreditation Committee ISCT-EBMT (JACIE) [51], which is aimed at promoting high quality patient care through the development of global standards and an internationally recognized system of accreditation. In the US, Foundation for the Accreditation of Cellular Therapy (FACT), together with the JACIE, have formed the JACIE-FACT that is now a unified, leading accreditation agency that insures high quality manufacture of therapeutics.

22.8 Aspects to Consider

Finally, a distinguishing feature of ATMPs deserves to be mentioned again: more than 90% of ATMP development resides in Academia and Small and Medium-sized Enterprises (SMEs). The academic environment has coined the field of ATMP development in many ways. Specific academic features include the close proximity to patients, limited resources in terms of funding, infrastructure and pharmaceutical development, a risk awareness and intentionality shaped sometimes more by disease and suffering than by quality considerations. Academic initiatives have engaged in networks and represent the non-canonical and decentralized developmental pathway of ATMPs [29, 34, 36]. The European Commission has recognized this development and, beyond project-related funding, reached out to and endorsed academic initiatives as a major stakeholder in the field.

22.9 Conclusions

As cell-based medicines often lose magic in the course of clinical development, so does the novelty assigned to ATMPs as the field matures. The development of ATMPs has shown immense success when large pharmaceutical companies have matched centralized models of manufacture and distribution with clinical efficacy (example: Kymriah et al.) [41]. Decentralized concepts, however, will continue to be paradigmatic for many cell-based medicines and to challenge the existing regulatory pathways. The regulatory bodies in the US as in the EU have responded to this demand, sometimes with similar concepts and harmonized incentives, sometimes with a regulatory framework that emerged on extensive stakeholder consultations to allow innovation to reach patients in need [52]. Yet the leading notion continues to be a picture of Europe lagging behind in the global thrive for advanced therapies, which have proven to have both a clinical and commercial potential. As the development of ATMPs cannot be regarded solely under market aspects and a cautious approach must also be considered to ensure patient safety, the EU fortunately continues to establish structures and platforms on a pre-competitive level where stakeholders from all sides are addressed [53]. At the same time, the complexity of ATMPs and the risk inherent in these medicinal products mandate a structured approach in terms of manufacture, application, and risk awareness in terms both clinical and quality risks. The ideal format of specialized, pre-competitive clusters will predominantly be:

1. associated with academic hospitals and centers;
2. defined by processes rather than products;
3. qualified and certified in a way that awaits definition; and
4. seek to find an interaction with industry in a way that respects both the transformative potential of ATMPs and the cautious position of industry that expects the risks inherent in ATMPs to become predictable to a certain extent.

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