Prospects of Advanced Therapy Medicinal Products and its Regulatory Approval Process IN US, EU, Japan, Australia and South Korea

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ABSTRACT:

The advent of advanced therapy medical products (ATMPs) to the global pharmaceutical market has revolutionized the pharmaceutical industry. These medicines have created new treatment options for numerous cancers and other terminal illnesses. The ATMPs are a class of sophisticated biological products that frequently require robust and in-depth preclinical, clinical, and testing for getting approval and placing the product in the market. Along with improvements in medical practice, scientific knowledge, and public acceptance of new technologies, the regulations regulating the use of medical goods for advanced treatments in humans, such as cell and gene therapy products have evolved. This review article seeks to give a general summary of the approval procedure for ATMPs in the America, Europe, Japan, South Korea, and Australia. PubMed, Google Scholar, and the websites of the relevant regulatory bodies were searched in order to assess published publications and guidance in this respect.

KEYWORDS: Advanced Therapy Medicinal Products, Biologics, Legislation and regulatory framework, Marketing Authorization, Cell and tissue based products.

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1. INTRODUCTION:

Recently the advancement in the area of regenerative medicines and biopharmaceuticals which has been using cells and tissues from the human body has been a gateway to the discovery of a novel and intellectual field known as the advanced therapy medicinal products[1] which has been the heart of concern to deal with diseases that has no effective treatment options[2][6]. The regenerative medicines can be defined as the "procedure used to create new, replace, or regenerate either human or animal cells and tissues in order to heal ailments and restore normal functionality". As per WHO the ATMPS are classified into four categories which is being explained on Table-1[8]. In Europe they are classified mainly into 3 categories as cell therapy, gene therapy and tissue engineered products[9]. Whereas in US unlike in EU the ATMPs are broadly classified and defined under the term Human cells and tissue based products (HCT/Ps)[10]. The ATMPs exhibit differences in regulation, approval process, scope and definition in different regulatory agencies[3]. The discovery of ATMPs has been transforming the worldwide pharmaceutical industry and opening up new treatment options for a number of chronic illnesses and tumors[4]. The ATMPs are a class of sophisticated biological products, and as such, they frequently require robust and in-depth both preclinical and clinical development and testing[5]. The areas in which ATMPS are used include injection of fibroblasts during cosmetic surgery, epidermal transplantation for emergency use, Activated mononuclear cell infusion for cancer treatment to chondrocyte injection for orthopedic trauma, transplantation of tissue engineered cartilage[7]. The aim of this article is to review the regulatory approval pathways for advanced therapy medicinal products in different countries like European Union, USA, Japan, Australia, South korea and Canada and point out the challenges and future perspectives of the ATMP products.

Classification	Definition	Field of Application
Gene therapy medicinal products	Anything made from a transgenic nucleic acid with the intention of regulating, mending, or altering a genome code	Cancer therapy Duchenne muscular dystrophy Neurodegenerative diseases Various genetic diseases like Hemophilia A and Huntington's
Somatic cell therapy products	comprises of cellular components or tissue components that have undergone significant alteration, resulting in changes to their biological features and physiological activities.	Parkinson's and Alzheimer's disease Defect of cartilage Skin replacement Cancer immunotherapy Immune disease
Tissue-	consists of synthetic cells or	Oesophagus made from tissue

engineered product	tissues provided to patients with the goal of replacing, rejuvenating, or restoring damaged human tissue.	engineering Trachea replacement Implantation of liver and kidney Small diameter vascular grafts
Combined ATMPs	Consists of viable cells/ tissues combined with one or more medical device in an effort to regenerate, repair, or replace human tissue	Long term diseases Cancer immunotherapy Inherited genetic diseases

TABLE 1: CLASSIFICATION, DEFINITION AND FIELD OF APPLICATION OF ATMPS AS PER WHO

2. MARKET TREND OF ATMPs:

As per the market analysis report the global market size of the ATMPs was valued $ 7.3 billion in 2021 and it is expected to reach a value of $17.4 billion USD with a 14.6% compound annual growth rate (CAGR) is projected between 2022 and 2030. US stands the largest contributor in both regional and global market[13]. The major force which is driving the ATMP market is the increase in R&D funding, increasing patient demand for new and innovative therapies and raising demand in cell and gene therapies for cancer treatment[14]. The high cost of the ATMP products are due to their critical manufacturing parameters and extensive clinical trials required to be done. As per Enrique Seoane- Vazquez et al., the manufacturers price for an ATMP product ranges from US $18,950 to US $1,206,751 for cell and gene therapy product. The prices for gene therapy products (US $357,309- US $1,206,751) are comparatively higher than cell therapy products (US $110,920- US $814,780) and tissue- engineering products (US $18,950- US $93,432)[15].

3. REGULATORY APPROVAL PROCESS OF ATMPs:

3.1 Regulations governing ATMPs in US:

Original attempts by the US Food and Drug Administration the principal regulatory authority that regulates pharmaceuticals[16] to address the products made from human cells and tissues regulations are based on changes to the already existing regulations for drugs, biologics and vaccines[17]. However, many type of cell and tissue based therapies are exempted in the regulation of HCT/Ps. This definition covers the Human Somatic Cell Therapy Products, a class of ATMPs. It is crucial to remember that no distinct product class has been established for tissue-based advanced medicines[11][12]. The Health Resource Service Administration regulates the BM with little manipulation and vascularized organs, Blood products and its derivatives falls under other regulations of FDA hence do not fall under the HCT/Ps[18]. In US the cell and gene therapy products were classified into HCT/Ps. After the issuance of the guidance in 1966 many rues and regulations regarding HCT/Ps have been implemented. The FDA proposed the 21 CFR 1271 which provides a comprehensive regulatory program for the

HCT/Ps in 1997[19]. Three categories—low risk, medium risk and high risk products—have been created from these HCT/Ps.

The low and medium risk products are referred to as “361 HCT/Ps” and they do not require any pre market approval. The requirements to be considered for getting an approval are listed as follows: a) the processing facility for the goods is permitted; b) informed consent form from the patients before using the product; c) complying with GMP, GLP, GCP and GTP; d) developing a system for product traceability; e) required documents and registration of the product and all the details about the test carried out and acquisition of materials[20].

While the sole class of high-risk products—referred to as "351 HCT/Ps"—requires pre-market clearance[21]. To get an approval for the high risk product the requirements to be considered are as follows: a) quality information including validation, stability and control of materials; b) compliance with GMP, GLP, GCP and GTP standards; c) clinical trial documents to prove the safety and effective of the treatment given[22].

The registration process for the HCT/Ps follows the approval process same as that of biologics. First the intended content of the application is recommended to discuss with relevant FDA review division and the relevant senior FDA officer will join the pre submission meeting. This meeting is conducted 2 months before making the original submission. After pre-BLA meeting original submission of the application is made by the applicant and within 60 days, the study's findings are publicised. Subsequently, on Day 74, a letter serving as notice to the applicant is delivered; it includes the anticipated date of the internal discussion for the mid-cycle evaluation, which takes place within five months and the results are released and the FDA then performs inspection to ensure that all GCP, GLP, and GMP programmes are in place within six months for priority applications and ten months for standard applications . Approval decision after review is determined within 12 months[23].

3.2. Regulations governing ATMPs in EU:

To govern ATMPs, a well developed legal framework is in place in EU. The EC sought to include the new class of biological medicine, cell and gene-based treatments under European pharmaceutical product regulation with Directive 2003/63/EC in June 2003 by revising the already existing directive 2001/83/EC. This was done to ensure the quality, safety, and efficacy of these products are in control[24]. Later in 2008, a separate Regulation on ATMPs—Regulation (EC) No. 1394/2007 was introduced amending Directive 2001/83/EC and Regulation (EC) No. 726/2004. After the implementation of the regulation 1394/2007, In 2009 the European Medicines Agency (EMA) formed the Committee for Advanced Therapies (CAT),an interdisciplinary expert panel, in recognition of the novel qualities of ATMPs[25].

Marketing Authorization Applications (MAA) of ATMPs are evaluated scientifically by the CAT and additionally, the CAT has been given two additional responsibilities, namely the certification of ATMPs and the ATMP categorization process[26]. The CAT evaluates the product registration dossier and recommends authorization or disapproval. Their choice is then evaluated and approved by the Committee for Medicinal Products for Human Use (CHMP). To obtain marketing authorization, ATMPs should follow and fulfil all the regulatory and scientific requirements like every other medical products[27].

Regulation (EC) No. 726/2004 mandates that the same centralised approval process, which takes 280 days, apply to ATMPs. The applicant sends the MAA to the EMA at the beginning of day 1. The CHMP coordinators and the EMA receive the assessment report from the CAT rapporteur and CO- rapporteur within 80 days of receipt. Then a list of questions (LoQ) has been prepared by the CHMP after clearly analyzing the report and the LoQ is sent to applicant within day 120. The clock stops until the applicant responds. After the submission of the response the clock starts again, the joint response assessment report is sent to the CAT, CHMP and EMA on day 150. On day 160 and 164 comments are received from PRAC, CAT and CHMP on joint CAT assessment report, The applicant receives notification from EMA of the list of "Outstanding Issues accepted by the CAT" within day 180. Clock stops and starts again after the response has been submitted, and if all flaws are rectified the CHMP issues a 30-day final opinion. Within 67 days of receiving a favorable opinion, the EC takes its final judgment[28][29].

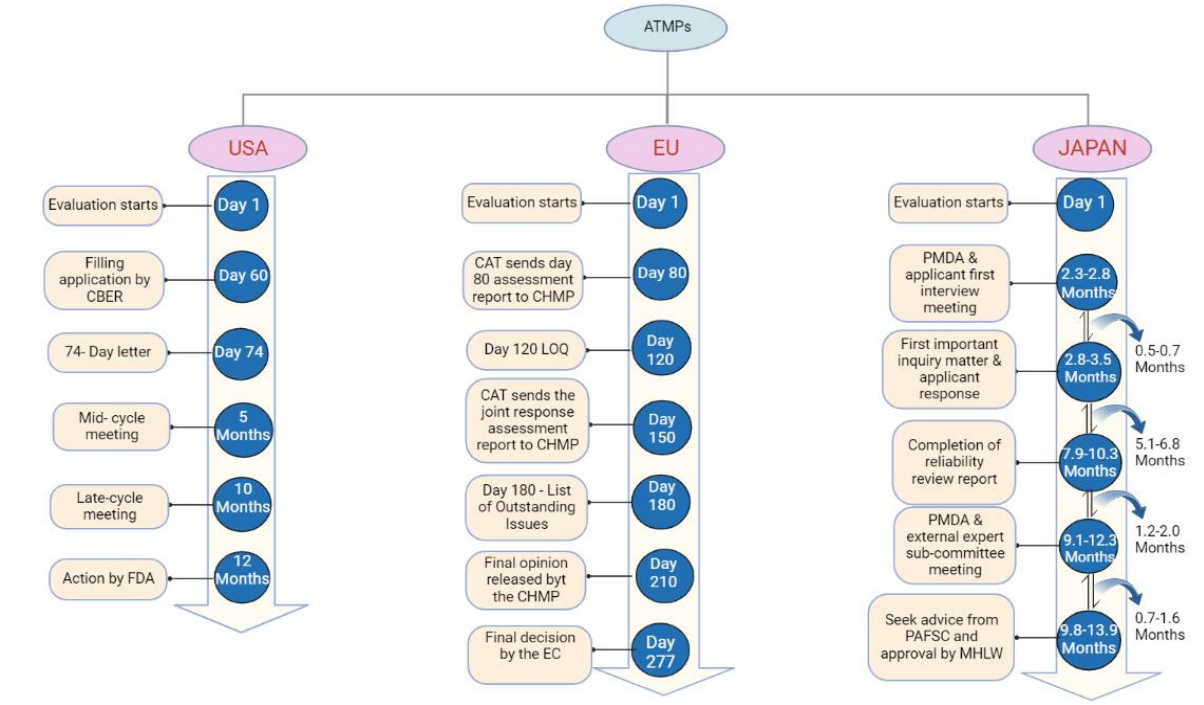

fig:1- regulatory approval process for USA, EU and Japan

3.3. Regulations governing ATMPs in Japan:

Regenerative cell treatments are a common name for ATMPs in Japan. On March 2013, the Japanese government was called to construct a well developed framework for Regenerative therapies and passed the Regenerative Medicine Promotion Act in May 2013[31] after the incident that caused the death of a korean patient who received treatment of stem cell which was processed outside Japan[30].The Act on the Safety of Regenerative Medicine (ASRM Act) and the Pharmaceutical Affairs Law (PAL) which was amended and now known as the Pharmaceuticals and Medical Devices Act (PMD Act) that came into effect from November 2013 are two new laws that supplement current. Conditional and expedited approval pathway was also included in the new PMDA[32]. Before any medical facility may provide regenerative medicine for class 3 and class 1&2 treatments, respectively, a Certified

Committee for Regenerative Medicine (CCRM) or Certified Special Committee for Regenerative Medicine (CSCRM) examination is necessary.

To conduct clinical trial for regenerative medicine, according to the PMDA the sponsor is required to submit the "Clinical Trial Notification". It takes upto 30 days for the PMDA to review the notification before accepting any clinical trials. Here, the quality and safety of the investigational product will be evaluated by the PMDA[33]. The GMP/GCP inspection team of The Office of Manufacturing Quality of Drugs (OQMD) is responsible for the evaluation of the production facility of the products. Based on the risk based approach the GMP inspection is conducted by two methods (i) Desktop examination that only looks at the information needed to ensure GMP adherence (ii) Inspection carried out on-site by the GMP/GCTP team[34].

It is suggested to obtain authorization from the minister of MHLW in order to bring a regenerative medicine in Japan. According to PMD Act the applications for market approval are reviewed by the PMDA, whereas the MHLW holds the final decision for approval. After examining the application information and the applicant's NDA, the authority contacts the applicant with a preliminary inquiry. The applicant is then invited to the first interview meeting. A reliability evaluation review is carried out after discussing the primary issues with external experts. The Pharmaceutical Affairs and Food Sanitation Council(PAFSC), an advisory group, and the MHLW are informed of the review's findings for review, following interaction between the PMDA and other specialists. The MHLW approves the final decision. Within a period of 12 months the review process is usually competed[35][36].

3.4. Regulations governing ATMPs in South Korea:

The Ministry of Food and Drug Safety (MFDS) is the authority responsible for approving pharmaceuticals in Korea[37]. The NIFDS which is a subsidiary headquarters has two divisions: The Advanced Medical Products Research Division is responsible of conducting quality checks and inquiries into ATMP regulatory procedures and the Cell and Gene Therapy Division is in charge of evaluating IND and NDA classified documents for ATMPs and obtaining approval to market. In 2019 the Act on Advanced Regenerative Medicine and Advanced Biopharmaceuticals which came into existence from 2020 provides a system for the support and commercialization of RM, enhance patient treatment options and strengthen safety management[38].In the absence of an effective alternative therapy and the application is intended to treat a critical or life-threatening condition, the MFDS may accelerate the examination of applied cell therapy applications in line with Article 36 of the act [39].

To get market approval for ATMP in Korea the process starts by submitting an IND application to the MFDS and is reviewed by a period of 30 days. The product that is subject to the IND application is inspected for GMP compliance prior to product approval. The laboratory and pharmacology data generated for the pre clinical studies must be in compliance with GLP. The IND is approved after submitting the approval of IRB, the clinical trial plan and the written informed consent form and the clinical trial is initiated in hospitals that are appointed as clinical trial institutions. On completing the clinical trial the NDA is filed and is reviewed within 115 days[40]. The evaluation process is put on hold if applicants are asked to submit further data; it restarts after a complete answer is given. Prior to

submitting the whole IND or NDA package, applicants can use a pre-review system to send sections of documentation addressing quality, safety, effectiveness, GMP considerations, and other concerns to the MFDS. While an IND and/or NDA are being evaluated, the MFDS may call a Central Pharmaceutical Affairs Advisory Committee (CPAC) meeting to seek expert advice on ethical and scientific issues. Then the MFDS holds the decision of approval[41][42].

3.5.Regulations governing ATMPs in Australia:

The Therapeutic Goods Administration (TGA), a major section of the Australian country's Department of Health, is the body in charge of overseeing the regulation of therapeutic items in that country. Biological products include those from tissue banks, stem cell therapies, and gene-modified cell treatments that are employed in human cell and tissue therapy. Simply, ATMPs falls under the regulatory framework of biologics[43]. Since there were no clear standards for cell and gene based products it was necessary to amend the original Therapeutic Goods Act. So the Regulatory framework for Biologicals was introduced and came into effect on June 2013, and requiring firms to comply by July 2014 and was updated recently on 2018[44].The framework lays out the legal framework for cell and gene based for export and import out or into Australia. This framework of biologics classifies the biologics into 4 categories on a risk-based approach :(i) Class I biologics are very low risk (ii) Class II biologics are low risk (iii) Class III biologics are medium risk (iv) Class IV biologics are high risk and are required to declare compliance with relevant standards, must be included in ARTG and should demonstrate cGMP compliance[45] .

Most of the Advanced therapy products falls under the class 2, 3 and 4 biologicals and the dossier required for authorization depends on the level of classification. Products used in in-vivo gene therapy that follow this regulatory mechanism of prescription medicine, with which the sponsor must comply with the standards outlined in the Guidelines for Australian Regulatory Compliance for Prescription Drugs.

By submitting a "New Biological Entity" application by the applicant to approval process begins. Within 30 days the preliminary evaluation is done and the results are announced by TGA. Then, on days 130, 180, and 230, each agency performs evaluations and requests data in line with Section 32 of the TG Act of 1989. The TGA contacts the Advisory Committee on Biologics (ACB) within 270 days, if needed. In total, the final authorization takes 290 days to complete[46].

Fast track clearance processes called "priority review" and "provisional approval" give some prescription drugs for illnesses that are significant or life-threatening accessing the Australian market more quickly. Considering the possibility of providing major benefits to patients, the sponsor may request time-limited provisional registration for a restricted number of promising new medications through the provisional approval process[47]. Prescription drug provisional registration through this procedure is permitted for a maximum of six years. By using this pathway a new product can make into the market 2 years earlier than for a normal approval process. For the priority review process the same quantity and kind of data is required as the usual review procedure. The TGA can complete the review at least three months sooner due to the more flexible evaluation process[48].

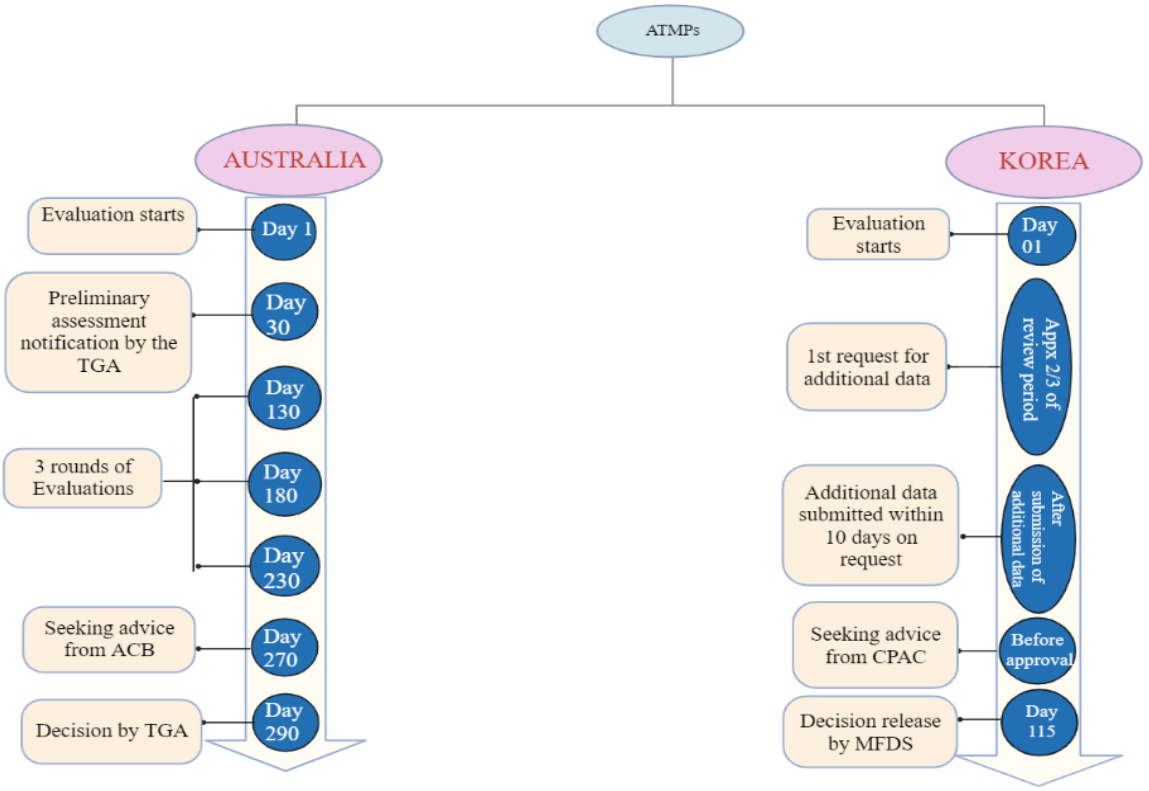

fig:2- regulatory approval process for Australia and Korea

4. PROSPECTS AND CHALLENGES ASSOCIATED WITH ATMP PRODUCTS:

The characteristics of the substance and the lack of pre-clinical data provide special challenges for the clinical development of ATMP. Additionally, the way they are administered may be invasive or necessitate the use of specialized equipment to place them in the human body, which raises additional quality assurance concerns regarding the administration procedure. For some indications, especially those involving life-threatening illnesses for which there is no adequate standard of care, the controlled or randomised trial may not be practical or morally acceptable[49]. In cell-based medicinal products finding the right cell markers might also be difficult because they are never always precise and directly related to cell function. Also finding an appropriate animal model can be difficult because, strictly speaking when receptors, cytokines and the microenvironment are taken into account, the human being is the sole relevant animal for evaluating human cells[50].Other main challenge of the Advanced therapies is the complex manufacturing and maintaining the quality control because in both cell and gene therapy products inconsistency was observed during the scale-up process[51]. Despite of these challenges possessed by ATMPs, they also offer various advantages such as it addresses complex diseases, provides highly personalized therapy, gives longer lasting effect and improves health related quality of life.

With the development of precise DNA editing tools, it is now possible to alter individual target sequence among the 6.4 billion base pairs that constitute the diploid human genome[52]. The ATMPs attribute a large portion of immunotherapy's success as a new paradigm to liberal clinical trial rules that consider the urgent need for treatments to improve cancer patients' quality of life after exhausting other treatment options as a requirement for

immunotherapy study enrolment[53]. ATMPs have paved the way advancement in treatment for hematologic disorders, orthopedic disorders, Immunologic disorders and especially in cancer therapy with the development of CAR-T cells[54].

5. CONCLUSION:

The road from the bench to human application may be long, filled with unforeseen curves and minefields, and each choice may have far-reaching effects. Researchers may create impactful impact statements, boost the relevance and applicability of their study, and forge strategic partnerships by understanding how their research can fit into the future and by following the guidelines, the product can be successfully launched in the market. It was possible to determine the review themes, such as effectiveness endpoints and long-term safety, that regulatory authorities were most interested in looking at when examining ATMP products for approval using the results of this study. We expect that with the harmonization of the review process for ATMPs, more products can enter into the market which will play a major role in treating a variety of diseases that doesn't have appropriate treatments.

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