



Original Article

Advanced Therapy medicinal products for autologous chondrocytes and comparison of regulatory systems in target countries



Jiwon Kim ^{a, b}, Jaehong Park ^{a, b}, Seung-Yeon Song ^b, Eunyoung Kim ^{a, b, *}

^a Department of Pharmaceutical Industry, Chung-Ang University, Seoul, 06974, Republic of Korea

^b Data Science, Evidence-Based Clinical Research Laboratory, Departments of Health Science & Clinical Pharmacy, College of Pharmacy, Chung-Ang University, Seoul, 06974, Republic of Korea

ARTICLE INFO

Article history:

Received 2 January 2022

Received in revised form

27 March 2022

Accepted 14 April 2022

Keywords:

Autologous chondrocytes

Advanced therapy medicinal products

ATMPs

HCT/Ps

ABSTRACT

Introduction: Autologous chondrocytes (ACs) are Human cell/tissue-based products used for the treatment of joint cartilage defects. Regulatory agencies have established regulations related to ACs to ensure their safety and efficacy. This study investigated the status and characteristics of ACs approved worldwide. Furthermore, the AC-related regulations were compared by country to provide reference materials for the development of product approval procedures.

Methods: This study reviewed the current status of global AC products over the past 20 years by referring to the AC approval list provided on the International Society for Cell & Gene Therapy (ISCT) website. Based on the review report provided by the regulatory agencies that approved the products, major nonclinical/clinical data and product characteristics were reviewed; and the classification and definition of ACs and the approval review procedures were compared through the regulatory agencies' websites. The development status of ACs was also analyzed using a clinical trial registration site.

Results: Eight ACs were approved during the study period in Europe, the US, Japan, Australia, and Korea. Two products were withdrawn owing to marketability problems. Human cell/tissue-based products in each country are classified and defined distinguished from biopharmaceuticals, but the approval process for both products is the same. The approval period differs by country, with an average of 282.4 days and the shortest being in Korea (115 days). On Clinical Trials.gov, we screened 46 clinical trials related to ACs, which were conducted in Europe (41%), Korea (20%), and the US (17%). The knee accounted for the largest portion of the indication (37/46, 80%), followed by the ankle or hip joints. Measurements of improvements in function and pain were the main endpoints used to evaluate the efficacy of ACs. Observational studies were conducted to confirm the long-term safety of these products.

Conclusions: This is the first study comparing the current status and characteristics of globally approved AC products, as well as their classification and definition by country. In the past two decades, clinical trials have been conducted on the application of ACs in tissue engineering to treat joint cartilage defects. ACs are expected to be used for the treatment of cartilage defect diseases.

© 2022, The Japanese Society for Regenerative Medicine. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Abbreviations: AC, Autologous chondrocyte; MF, Microfracture; ACI, Autologous chondrocyte implantation; EU, European Union; US, United States; ISCT, International Society for Cell & Gene therapy; EMA, European Medicine Agency; FDA, Food and Drug Administration; CBER, Cellular, Tissue, and Gene Therapies Advisory Committee; PMDA, Pharmaceuticals and Medical Devices Agency; TGA, Therapeutic Goods Administration; MFDS, Ministry of Food and Drug Safety; ICRS, International Cartilage Regeneration & Joint Preservation Society; KOOS, Knee injury and Osteoarthritis Outcome; VAS, Visual Analogue Scale; MOCART, Magnetic resonance Observation of Cartilage Repair Tissue; ATMPs, Advanced therapy medicinal products; EC, European Commission; CAT, Committee for Advanced Therapies; CHMP, Committee for Medicinal Products for Human Use; HCT/Ps, Human cells, tissues, and cellular and tissue-based products; CFR, Code of Federal Regulation; MHLW, Ministry of Health, Labor, and Welfare; PAFSC, Pharmaceutical Affairs and Food Sanitation Council; ACB, Advisory Committee on Biologicals; CPRC, Central Pharmaceutical Affairs Council; TEPs, Tissue Engineered Products; PHS, Public Health Service; PMD, Pharmaceutical and Medical Device.

* Corresponding author. Division of Licensing of Medicines and Regulatory Science, The Graduate School of Pharmaceutical Management, Chung-Ang University, 84 Heukseok-Ro, Dangjak-gu, Seoul, 06974, Republic of Korea. Tel: +82-2-820-5791, Fax: +82-2-816-7338.

E-mail address: eykimjcb777@cau.ac.kr (E. Kim).

Peer review under responsibility of the Japanese Society for Regenerative Medicine.

<https://doi.org/10.1016/j.reth.2022.04.004>

2352-3204/© 2022, The Japanese Society for Regenerative Medicine. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

The innovative industry of biopharmaceuticals utilizing tissues and cells derived from the human body is continuously growing worldwide. As of 2018, the total revenue of the pharmaceutical market was estimated to be \$864 billion, and the revenue of the biopharmaceutical market was estimated to be \$243 billion, accounting for 28% of the total pharmaceutical market, and is expected to increase to 32% by 2024 [1]. However, owing to health and hygiene concerns, the application of existing synthetic drugs is limited; therefore, overseas regulatory agencies have recently established regulations to ensure the safety and efficacy of biopharmaceuticals and implement various policies to promote the development.

Autologous chondrocytes (ACs) have been actively developed since the late 1990s as a response to the increasing number of cases of joint cartilage defects among the aging population [2]. Cartilage defects, known to occur in approximately 12% of the total population, are caused by traumatic or degenerative diseases, which are unlikely to be cured naturally [3]. Overall, unlike degenerative arthritis in which the cartilage is worn, in the case of cartilage defects, only the healthy joint cartilage is maintained in the periphery of the lesion; therefore, treatment is aimed to replace only the defective area with healthy cartilage. Treatment includes microfracture (MF) and AC implantation (ACI). In MF therapy, holes are finely drilled in the bones exposed to cartilage damage areas so that cartilage-producing cells in the bone marrow induce natural healing. In ACI therapy, ACs are transplanted. If the defect area is too large, Autologous Osteochondral Transplantation (AOT) can be considered. However, even the latest treatments, including stem cell therapy, still cannot completely replace the defect site [4].

ACs are an innovative and complex product that can meet current medical needs. Unlike mass-produced synthetic drugs, ACs are patient-specific products in which cells isolated from donors are manipulated, cultured, and injected back into the patient. However, despite their advanced but unfamiliar technology, these products must be evaluated for safety and efficacy through clinical trials before their application in donors, and this process requires considerable time and cost. Therefore, regulatory agencies have established regulations to promote the development of ACs.

Although AC products have been developed, approved, and used in many countries, experience and data on the safety and efficacy of ACs are still lacking compared with that of previously developed synthetic drugs [5]. The regulatory systems implemented by regulatory agencies are different between countries, and analyzing these systems will be helpful for collecting nonclinical and clinical data generated during the development and approval process of AC products. Recently, studies comparing AC development status [6], clinical progress [7], and regulatory frameworks for tissue-based products have been published [8], but no studies have compared the overall regulatory status of ACs, such as the related national approval procedures, classification, and definition.

This study investigated the global status and characteristics of AC products and compared the regulations implemented by the regulatory agencies that authorized the products. The findings of this study will provide reference materials for the development of product approval procedures.

2. Methods

The status of approved AC products in the European Union (EU), the United States (US), Japan, Australia, and Korea over the past 20 years from October 7, 2001, to October 7, 2021 was investigated. Major nonclinical and clinical trials and product-specific characteristics were summarized. In addition, the marketing authorization procedure, classification, and definition of ACs were compared and reviewed

through the website of the regulatory agencies that approved the products. The development status of ACs was also analyzed until October 7, 2021, using the clinical trial registration site.

AC products approved between October 7, 2001, and October 7, 2021, were screened from the websites of regulatory agencies in major countries, such as European countries, the US, Japan, Australia, and Korea, referring to the latest Cell, Tissue and Gene Products approvals published in February 2021 by the International Society for Cell & Gene Therapy (ISCT).

Major nonclinical and clinical trials carried out before and after approval and the product-specific characteristics were referred to as product review reports by regulatory agencies. The regulations, classifications, and definitions of the products were confirmed through the websites of the regulatory agencies.

The regulatory agency of the EU is the European Medical Agency (EMA) [9–11]. Product information, in the form of public assessment reports, and related regulations were obtained from the EMA website.

The US regulatory agency is the Food and Drug Administration (FDA) [12]. Product information and the related regulations were acquired from the FDA website. A list of approved cellular and gene therapy products was attained from the Center for Biologics Evaluation and Research (CBER).

The Pharmaceutical and Medical Devices Agency (PMDA) is a regulatory agency in Japan [13]. Product information, in the form of product review reports, and related regulations were obtained from the PMDA website.

The Therapeutic Goods Administration (TGA) is a regulatory agency in Australia [14]. Product information and related regulations were confirmed on the TGA website.

The Korean regulatory agency is the Ministry of Food and Drug Safety (MFDS). Product information was obtained from drug information system sites [15,16] and the approval review report [17,18] of each product. Related regulations were attained from the MFDS website.

Clinical status was searched on [ClinicalTrials.gov](https://www.clinicaltrials.gov) using the term “autologous chondrocytes” (as of October 7, 2021). The data were analyzed by lesion, product name, country, registration year, study phase, sample size, study sponsor, and study status. Overlapping results were excluded.

3. Results

3.1. Approved autologous chondrocyte products in the EU, the US, Japan, Australia, and Korea

3.1.1. Autologous chondrocyte products authorized worldwide

In the last 20 years, eight AC products have been approved, namely, three European products, one US product, one Japanese product, one Australian product, and two Korean products (Table 1). Most of AC products for knee cartilage defects were approved for administration to patients with International Cartilage Regeneration & Joint Preservation Society (ICRS) grade III or IV. The area of application differed by product, except for nonspecific cases, which ranged from 2 to 20 cm². ChondroCelect® and MACI® (approved in the EU) were withdrawn from the market, whereas Spherox®, JACC®, Chondrocytes-T-Ortho-ACI®, and Cartilife® are currently being subjected to additional safety investigations as part of post-marketing surveillance.

3.2. Regulatory action for pre-/post-approval evaluation in the EU, Japan, and Korea

The major nonclinical and clinical trials conducted before and after the approval of the eight AC products are summarized in

Table 2. Chondrocytes-T-Ortho-ACI®, for which a review report was not published, and MACI®, which was approved by the FDA with the same data submitted to the EMA, were excluded.

The approved products were compared mainly using Knee injury and Osteoarthritis Outcome Score (KOOS) [Appendix I], a functional and pain improvement evaluation method based on patient reports, with patients who underwent MF surgery as an active control in the pivotal study.

In the case of Chondron®, the visual analogue scale (VAS) was used to evaluate the degree of pain as the primary outcome [19]. The Knee Society Score (KSS), which evaluates pain and functional conditions, was also examined as a secondary outcome [20].

In the case of Cartilife®, cartilage damage was measured using magnetic resonance imaging (MRI), and the primary outcome was magnetic resonance observation of cartilage repair tissue (MOCART) [Appendix III]. Lysholm knee score, KOOS, International Knee Documentation Committee (IKDC), VAS, and range of motion (ROM) were also confirmed as secondary outcomes.

3.3. Technological characteristics of autologous chondrocyte products

3.3.1. Evolution of autologous chondrocyte implantation therapy

Owing to the shared structural and biomechanical features between ACs and endogenic hyaline cartilages, ACI promotes the production of regenerative tissues [21]. The main purpose is to replace or repair cartilage defects. Surgical procedures were attempted in humans for the first time in 1994 as a treatment in which healthy cartilage cells of patients were collected using arthroscopy, cultured for 14–21 days, and transplanted into the defective area [22]. Carticel®, the first commercial ACs, was approved by the FDA in 1997 [23].

According to a review by Davies et al., first-generation ACI involves culturing knee chondrocytes in a monolayer. Before the cultured cells mixed with the solution were injected, autologous periosteal patches extracted from the tibia were transplanted into the lesion area to prevent solution leakage. This enable the surgeon to inject the cell suspension into periosteal patch. However, periosteum hypertrophy can occur in these processes.

Table 1
Autologous chondrocyte products for articular cartilage defects.

Product name	Approval date	Marketing authorization holder	Regulatory agency	Indication		Regulatory Status
				Lesion	Area of application	
ChondroCelect®	October 2009	TiGenix N.V.	EMA/CHMP	Femoral condyle of the knee (ICRS grade III or IV)	Not determined	^a November 2016
MACI®	June 2013	Vericel Corporation	EMA/CHMP	Knee (Modified Outerbridge Scale grade III and IV)	3–20 cm ²	^a September 2014
Spherex®	July 2017	CO.DON AG	EMA/CHMP	Femoral condyle and patella of the knee (ICRS grade III or IV)	Up to 10 cm ²	^b Post-authorization study
MACI®	Dec 2016	Vericel Corporation	FDA/CBER	Knee	Not determined	In the market
JACC®	July 2012	Japan Tissue Engineering Co., Ltd.	MHLW-PMDA	Knee	≥4 cm ²	^b Post-authorization study
Chondrocytes-T-Ortho-ACI®	March 2017	Orthocell, Ltd.	TGA	Knee, patella, and ankle (ICRS grade III or IV)	Not determined	^b Post-authorization study
Chondron®	August 2021 (January 2001)	CELLONTECH Co., Ltd.	MFDS	Knee	Single lesion ≤15 cm ² Multiple lesions ≤20 cm ²	In the market
Cartilife®	August 2021 (April 2019)	Biosolution, Co., Ltd.	MFDS	Knee (ICRS grade III or IV)	2–10 cm ²	^b Post-authorization study

EMA, European Medicines Agency; CHMP, Committee for Human Medicinal Products; FDA, Food and Drug Administration; CBER, Center for Biologics Evaluation and Research; MHLW, Ministry of Health, Labor, and Welfare; PMDA, Pharmaceuticals and Medical Device Administration; TGA, Therapeutic Goods Administration; MFDS, Ministry of Food and Drug Safety; ICRS, International Cartilage Regeneration & Joint Preservation Society.

^a Withdrawn by company request.

^b MA under considerable obligations.

This was solved by the development of Chondro-Gide®, a second-generation ACI that fills cartilage-damaged areas with gel-type treatments rather than cartilage cells. Instead of a micro-periosteal patch, a porcine collagen type I/III membrane was attached to the perforated areas to help differentiate the cartilage cells.

However, there is a disadvantage that it is difficult to observe the long-term treatment effects, as the damaged area is filled without AC culture and transplantation process. Matrix-induced chondrocyte implantation, a third-generation ACI, overcomes the limitations of the first and second generations. In this ACI, chondrocytes are cultured in hydrated scaffolds and then transplanted into the cartilage-damaged areas [24]. The third-generation ACI has the advantage of shorter surgical and hemostasis times than those of conventional treatments, and it enables minimally invasive transplantation [22]. Cartilife® is a fourth-generation ACI in which pellet-type chondrocyte tissue is implanted without a scaffold, further shortening the rehabilitation period because side effects such as foreign body reactions are fewer, and there is no need to wait for the implanted cells to harden [18].

3.3.2. Technological characteristics of approved autologous chondrocyte products

The technological characteristics of the eight approved products are summarized in Table 3.

ChondroCelect® is transplanted as pellets differentiated into cartilage tissues through three-dimensional culture; additional measures such as osteotomy are needed to prevent leakage after transplantation [9].

In the case of MACI®, normal cartilage cells collected from donor tissues were cultured as a monolayer culture for approximately 4 weeks. Subsequently, the cultured chondrocytes are transferred to a collagen type I/III membrane (ACI-Maix™) scaffold, cultured for several days, and transplanted into the defect site. ACI-Maix™ has been classified as a medical device [10].

Spherex® is cultured in a monolayer cell culture with donor tissue composed of normal chondrocytes and then transplanted into the extracellular matrix, resulting in a three-dimensional spheroid form [11].

Table 2
Pre- and post-approval clinical evaluations of autologous chondrocyte products.

Country or area	Product name	Nonclinical studies	Clinical studies					Post-approval evaluation
			Pre-approval evaluation					
			Year	Phase	Design and follow-up period	Setting and sample size	Principal outcomes	
EU	ChondroCelect®	<ul style="list-style-type: none"> Bone growth at the defect site was observed at week 52 in a goat pharmacological study. Single-dose toxicity studies in nude mice and sheep. Carcinogenicity assay of ChondroCelect® culture after serial passaging. 	2006	III	RCT: patients treated with ACI vs patients treated with MF at 12, 18, and 60 months post-surgery	EU, 118 patients: 57 treated with ChondroCelect® and 61 with MF	<ul style="list-style-type: none"> Primary outcome: KOOS Average change from baseline in total KOOS: ChondroCelect® group, 16.18 ± 2.42; MF group, 14.37 ± 2.35 [Difference (95% CI): 1.81 (−3.28, 6.90)] 	Pharmacovigilance activities (5-year long-term safety and efficacy)
	MACI®	<ul style="list-style-type: none"> Tissue regeneration was observed at week 53 in rabbit, sheep, and horse pharmacological studies. Single-dose toxicity studies in mice and horse. Chromosomal stability testing was conducted in human chondrocytes. 	2008	III	RCT: patients treated with ACI vs patients treated with MF at 24 and 60 months post-surgery	EU, 144 patients: 72 in each study group	<ul style="list-style-type: none"> Primary outcome: KOOS Average change from baseline in KOOS: MACI® group, 45.45 ± 21.08; MF group, 46.04 ± 28.35 (p < 0.05) 	Pharmacovigilance activities (5-year long-term safety and efficacy)
	Spherox®	<ul style="list-style-type: none"> In a merino sheep pharmacological study, spheroids had filled and integrated well in the defect area at 2 months, and there was no difference in the defects treated with and without spheroids at 9 months. 	2010	II	Uncontrolled clinical trial: patients treated with ACI (three doses) at 12 and 60 months post-surgery	EU, 73 patients: high-dose group, 24 patients; medium-dose group, 25 patients; low-dose group, 24 patients	<ul style="list-style-type: none"> Primary outcome: KOOS Time course of the overall KOOS changes was similar between three dose groups 	Pharmacovigilance activities (5-year long-term safety and efficacy)
		2010	III	RCT: patients treated with ACI vs patients treated with MF at 12 and 60 months post-surgery	EU, 102 patients: 52 treated with Spherox® and 50 with MF	<ul style="list-style-type: none"> Primary outcome: KOOS Average change from baseline KOOS: Spherox® group, 22.2 ± 18.3; MF group, 16.4 ± 15.1 (p < 0.0001) 		
Japan	JACC®	<ul style="list-style-type: none"> In a dog pharmacological study, positive areas were observed in the defect sites at 26 and 53 weeks. 	2004	III	Uncontrolled clinical trial: patients treated with ACI at 12 and 51 months post-surgery	30 patients	<ul style="list-style-type: none"> Primary outcome: comprehensive knee function and arthroscopic assessments^a Improvement from baseline: 83.3%, very effective; 10%, effective; 6.7%, neither effective nor ineffective; 0%, ineffective 	Post-market survey for all patients treated with JACC® for 7 years
Korea	Chondron®	<ul style="list-style-type: none"> Improved repair at 12 weeks compared to that in the first-generation ACI in a dog pharmacological study. 	2006	III	Uncontrolled clinical trial: patients treated with ACI for 24 months	17 patients	<ul style="list-style-type: none"> Primary outcome: VAS Mean VAS declined from 52.24 ± 23.5 to 19.91 ± 23.59 mm (p = 0.00) 	Pharmacovigilance activities for 4 years
	Cartilife®	<ul style="list-style-type: none"> Single-dose toxicity study in rabbits In a study in nude mice, bonding between the graft bone and the regenerated cartilage was observed at the 4th week of transplantation. 	2018	I	Uncontrolled clinical trial: patients treated with ACI for 48 weeks	7 patients	<ul style="list-style-type: none"> Primary outcome: safety Adverse reactions occurred in 5 out of 7 subjects, but not related to the test drug and were mild 	Pharmacovigilance activities for 6 years
			<ul style="list-style-type: none"> Regenerated tissue formation was observed at 24 weeks in the a goat study. 	2018	II	Randomized clinical trial: patients treated with ACI vs patients treated with MF for 48 weeks	30 patients: 20 treated with Cartilife® and 10 with MF	<ul style="list-style-type: none"> Primary outcome: MOCART scores Average change from baseline in MOCART scores: Cartilife® group, 43.00 ± 13.12; MF group, 24.75 ± 19.74 (p = 0.0052)

EU, European Union; US, United States; RCT, randomized clinical trial; ACI, autologous chondrocyte implantation; MF, microfracture; KOOS, Knee injury and Osteoarthritis Outcome Score; VAS, Visual Analogue Scale; MOCART, Magnetic Resonance Observation of Cartilage Repair Tissue.

^a Comprehensive knee function and arthroscopic assessments: refer to [Appendix II](#).

Table 3
Comparison of the features of approved autologous chondrocyte products.

Approval year	Product name	Usage	Need of a periosteal patch	Scaffold
2001	Chondron®	Transplantation after culture of donor tissues in fibrin gel	O	O (fibrin gel)
2009	ChondroCelect®	Transplantation of pellets differentiated into cartilage tissues through 3D culture	O	X
2012	JACC®	Transplantation after culture of donor tissues in atelocollagen gel	X	O (atelocollagen gel)
2013	MACI® ^a	Transplantation after culture of donor tissues in collagen membrane	X	O (collagen membrane)
2017	Chondrocytes-T-Ortho-ACI®	Transplantation after culture of donor tissues in collagen membrane	X	O (collagen membrane)
2017	Spherox®	Transplantation after culture of donor tissues as spheroids in monolayer cell culture	X	X
2019	Cartilife®	Transplantation of pellets differentiated into cartilage tissues through 3D culture	X	X

^a MACI® was approved by both the EMA and FDA, and the data were obtained from the EMA assessment report.

JACC® is a product in which donor tissue comprising normal chondrocytes is cultured in atelocollagen for approximately 4 weeks and then transplanted into the bone membrane in the defective area [13]. Since 2019, JACC® has been modified to use collagen membrane instead of periosteum to minimize invasive transplant procedure.

Chondrocytes-T-Ortho-ACI® is a product in which healthy chondrocytes are cultured and transplanted into collagen scaffolds and cultured for approximately 5 weeks [25].

Chondron®, the first AC approved in Korea, is a treatment in which cartilage cells are cultured for 4–6 weeks using fibrin gel, not a solution, to overcome the shortcomings of first-generation ACI. Using a collagen membrane scaffold can eliminate the need for a second incision for periosteal harvest and reduce the surgical time. However, with this method there are also some potential problems such as the loss of critical chondrocytes caused by cutting and repeated manipulation of the seeded membrane. There is also the possibility of detachment of the collagen membrane from the cartilage defect [26].

Cartilife® is a product in which donor tissue is collected from the rib cartilage of a patient and then cultured for 6–7 weeks to generate pellets containing cartilage cells and extracellular substrates, which are then transplanted to the defective area [18].

3.4. Marketing authorization procedure for autologous chondrocytes in the EU, the US, Japan, Australia, and Korea

3.4.1. Regulatory frameworks for ATMPs in the EU

ACs are classified Advanced therapy medicinal products (ATMPs) in the EU. The approval process for ATMPs was the same as that for the centralized approval process according to the Regulation European Commission (EC) No 726/2004 (Fig. 1). As stated in the ATMP Regulation (EC) No 1394/2007, the scientific evaluation of marketing authorization applications (MAAs) for ATMPs is primarily performed by the Committee for Advanced Therapies (CAT).

Within 80 days after receipt of approval application, CAT rapporteurs send a report to the Committee for Medicinal Products for Human Use (CHMP) which is an evaluation report focusing on Risk Management Plan (RMP) evaluation related to long-term safety and efficacy studies. After critically analyzing this report, the CHMP prepares a list of questions (LoQ) before day 120 and sends it to the applicant. The review process stops when the applicant submits an answer. After the applicant submits the answer (day 121), review is then conducted before day 180, and on day 150, the CAT sends a Joint Response Assessment Report (JAR) to the CHMP. Within 180 days, a list of outstanding issues (LoOI) is sent to the applicant, and

if all issues are resolved, the CHMP states its final opinion within 30 days. If the opinion is positive, the EC makes its final decision within 67 days [27].

3.4.2. Regulatory frameworks for HCT/Ps in the US

ACs are classified as human cells, tissues, and cellular and tissue-based products (HCT/Ps) in the US. The approval process for HCT/Ps is the same as that for biological drugs, in accordance with Title 21 of the Code of Federal Regulations (CFR), Part 601: Licensing (Fig. 2). When the applicant submits the Biologic License Application (BLA), the CBER conducts a review. The results of the review are released within 60 days, and a Day-74 Letter is delivered to the applicant within 74 days. An interim meeting is held within 5 months, and the results of the review are revealed. A final meeting is held 2 months before the final approval. Thus, the approval decision is determined within a total of 12 months [28].

3.4.3. Regulatory frameworks for regenerative cell therapy in Japan

ACs are classified as regenerative cell therapies in Japan. After the approval application is submitted, the PMDA will review the product, and then the Ministry of Health, Labor, and Welfare (MHLW) will make the final decision (Fig. 3). When an applicant submits the New Drug Application (NDA), the PMDA sends preliminary inquiries to the applicant after reviewing the application data and then holds the first interview meeting with the applicant. After discussing the main problems with external experts, a reliability assessment review is conducted. After consultation between the PMDA and external experts, the results of the review are reported to the MHLW for consultation with the Pharmaceutical Affairs and Food Sanitation Council (PAFSC), which is the advisory committee. The final approval is authorized by the MHLW [29]. The mean time required from application receipt to approval is shown in Fig. 3. In general, the review is completed within 12 months [30].

3.4.4. Regulatory frameworks for biologicals in Australia

ACs are classified as biologicals in Australia. The approval procedure begins after an applicant submits an approval application called a “New Biological Entity” (NBE) (Fig. 4). Within 30 days, the TGA notifies the results of the preliminary assessment. Next, reviews are conducted by each department, and data are requested in accordance with Section 32 of the Therapeutic Goods Act 1989 (on day 130, 180, and 230). Within 270 days, the TGA consults the Advisory Committee on Biologics (ACB), if necessary. The final approval is concluded within a total of 290 days [8].

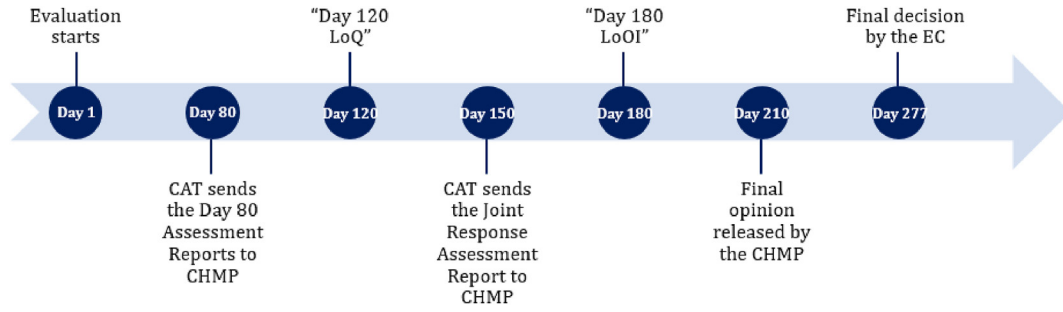


Fig. 1. Authorization review process for ATMPs in the EU. ATMP, Advanced therapy medicinal products; EU, European Union; CAT, Committee for Advanced Therapies; CHMP, Committee for Medicinal Products for Human Use; LoQ, list of questions; LoOI, list of outstanding issues; EC, European Commission.

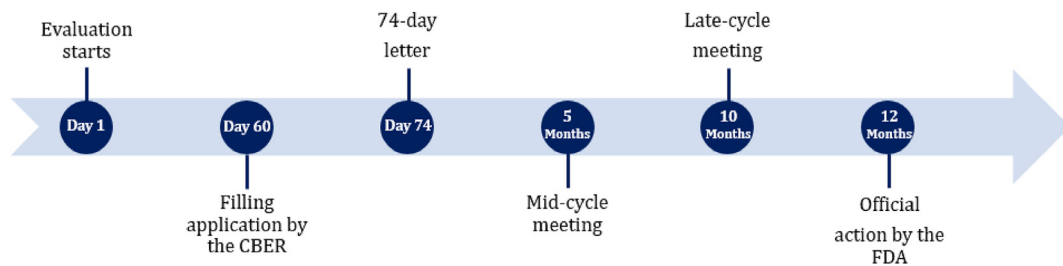


Fig. 2. Authorization review process for HCT/Ps in the US. HCT/Ps, Human cells, tissues, and cellular and tissue-based products; US, United States; CBER, Center for Biologics Evaluation and Research; FDA, Food and Drug Administration.

3.4.5. Regulatory frameworks for ATMPs in Korea

ACs are classified as ATMPs in Korea. The ATMP approval process is conducted in accordance with the Advanced Regenerative Medicine and Advanced Biopharmaceutical Safety and Support Act, as that for biopharmaceuticals (Fig. 5). After an applicant submits an NDA, a review period of 115 days is commenced. During the review, supplementary requests may occur up to two times, and the first supplement can be extended up to two times; however, in the case of the second supplement, supplementary submission must be completed within 10 days without extension. The review is suspended from the time a supplementation is requested to the time of its submission. If needed, the MFDS can seek advice from an advisory committee called the Central Pharmaceutical Review Committee (CPRC) during the review [31].

3.5. Classification and definition of autologous chondrocyte products in the EU, the US, Japan, Australia, and Korea

The table below summarizes the classification, definition, and comparison of approval procedures by different regulatory agencies for the eight AC products (Table 4).

The classification and definition of AC products are summarized in Table 5.

In the EU, Regulation (EC) No 1394/2007 Article 2(1) (a) defines gene therapy, somatic cell therapy, and tissue-engineered products (TEPs) as ATMPs. Among ATMPs, drugs aimed at regenerating, restoring, or replacing tissues are defined as TEPs according to Regulation (EC) No 1394/2007 Art 2(1) (b). Regulation (EC) No 1394/2007 Article 2(3) also includes autologous and allogeneic cell therapies as ATMPs. ACs approved in Europe to date have been classified as TEPs among ATMPs owing to their association with tissue regeneration, restoration, or substitution.

In the US, ACs are classified as HCT/Ps. In 21 CFR 1271.3(d), treatments using human cells, tissues, and tissue engineering are defined as HCT/Ps. If an HCT/P does not meet the conditions of 21 CFR 1271.10(a), it will be classified as a biopharmaceutical and subject to Section 351 of the Public Health Service (PHS) Act, and product review will be conducted by the CBER.

Japan defines regenerative medicine products in the Pharmaceutical and Medical Device (PMD) Act Chapter 1, Article 2, and paragraph 2, and ACs correspond to the described definition.

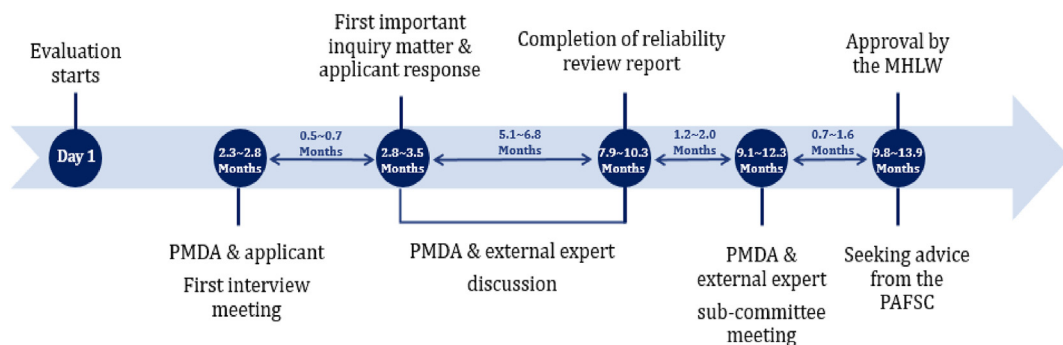


Fig. 3. Authorization review process for regenerative medicine products in Japan. PMDA, Pharmaceuticals and Medical Devices Agency; PAFSC, Pharmaceutical Affairs and Food Sanitation Council; MHLW, Ministry of Health, Labor, and Welfare.

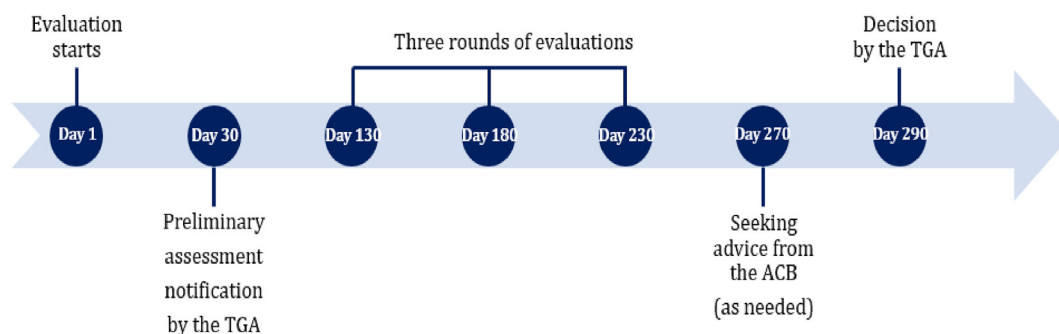


Fig. 4. Authorization review process for biologicals in Australia. TGA, Therapeutic Goods Administration; ACB, Advisory Committee on Biologicals.

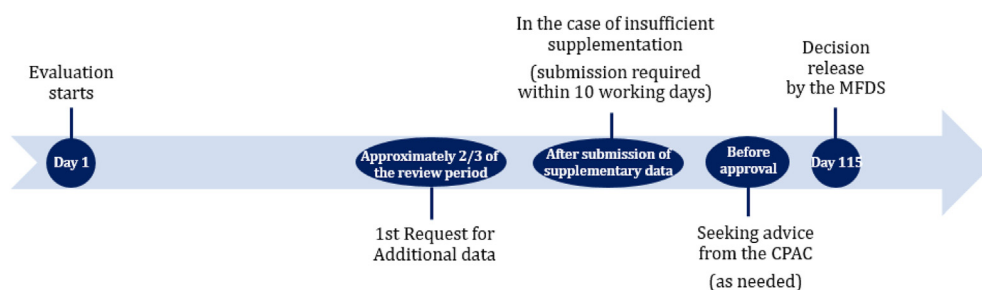


Fig. 5. Authorization review process for ATMPs in Korea. CPAC, Central Pharmaceutical Affairs Council; MFDS, Ministry of Food and Drug Safety.

In Australia, ACs are classified as biologicals in the Therapeutic Goods Act 1989 Part 3. Moreover, in the Australian Regulatory Guidelines for Biologics (ARGB), a regulation for autologous human cell and tissue products, autologous human cell and tissue products are defined as “those that comprise, contain, or are derived from human cells and tissues and removed from, and applied to, the

same person.” ACs are classified as biologicals and are fully regulated by TGA [32].

In Korea, cell therapy is defined in Article 2 of the Safety and Support of Advanced Regenerative Medicine and Advanced Therapy Medicinal Products Act. To date, all ACs approved in Korea are classified as cell therapy products (Table 5).

Table 4

Comparison of AC products: classification according to regulatory agencies, regulations related to definition, advisory committee, decision-making committee, and period to approval.

Product name	Country or area	Regulatory agency	Classification	Regulation related to definition	Advisory committee	Decision-making committee	Procedure period (days)
ChondroCelect®	EU	EMA	TEP	Regulation (EC) No 1394/2007 Article 2(1) (b)	CAT	CHMP	277
MACI®	EU	EMA	TEP	Regulation (EC) No 1394/2007 Article 2(1) (b)	CAT	CHMP	365
Spheriox®	EU	EMA	TEP	Regulation (EC) No 1394/2007 Article 2(1) (b)	CAT	CHMP	290
MACI®	US	FDA	HCT/Ps	PHS Act 351 and 21 CFR 1271.10(a)	CTGTAC	CBER	365
JACC®	Japan	MHLW	Regenerative medicine product	PMD Act Chapter 1, Article 2	PAFSC	MHLW	N/A (Aim to 365)
Chondrocytes-T-Ortho-ACI®	Australia	TGA	Biological	Therapeutic Goods Act 1989 Part 3-2A	ACB	TGA	290
Chondron®	Korea	MFDS	Cell therapy product	Act on the Safety and Support of Advanced Regenerative Medicine and Advanced Therapy Medicinal Products, Article 2	CPAC	MFDS	115
Cartilife®	Korea	MFDS	Cell therapy product	Act on the Safety and Support of Advanced Regenerative Medicine and Advanced therapy Medicinal Products, Article 2	CPAC	MFDS	115

EU, European Union; EMA, European Medicine Agency; TEPs, tissue-engineered products; EC, European Commission; CAT, Committee for Advanced Therapies; CHMP, Committee for Medicinal Products for Human Use; US, United States; FDA, Food and Drug Administration; HCT/Ps, human cells, tissues, and cellular and tissue-based products; PHS, Public Health Service; CFR, Code of Federal Regulation; CTGTAC, Cellular, Tissue and Gene Therapies Advisory Committee; CBER, Center for Biologics Evaluation and Research; MHLW, Ministry of Health, Labor, and Welfare; PMD, Pharmaceuticals and Medical Devices; PAFSC, Pharmaceutical Affairs and Food Sanitation Council.

Table 5
Classification and definition of autologous chondrocyte products in the EU, the US, Japan, Australia, and Korea.

Country or area	Classification	Definition	Regulation
EU	ATMPs	<ul style="list-style-type: none"> Any of the following medicinal products for human use: a gene therapy medicinal product, a somatic cell therapy medicinal product, or a tissue engineered product 	Regulation (EC) No 1394/2007 Article 2(1) (a)
	TEPs	<ul style="list-style-type: none"> A product that: contains or consists of engineered cells or tissues, or is used in or administered to human beings with a view to regenerating, repairing, or replacing a human tissue A tissue-engineered product that may contain cells or tissues of human or animal origin, or both 	Regulation (EC) No 1394/2007 Article 2(1) (b)
US	HCT/Ps	<ul style="list-style-type: none"> HCT/Ps mean articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. An HCT/P is regulated solely under section 361 of the PHS Act and the regulations in this part if it meets all of the following criteria: <ul style="list-style-type: none"> minimally manipulated intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent the manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P either (1) the HCT/P does not have a systemic effect and is not dependent on the metabolic activity of living cells for its primary function, or (2) the HCT/P has a systemic effect or is dependent on the metabolic activity of living cells for its primary function, and - intended (a) for autologous use, (b) for allogeneic use in a first- or second-degree blood relative, or (c) for reproductive use 	21 CFR 1271.3(d)
		<ul style="list-style-type: none"> Processed human or animal cells intended for either: <ul style="list-style-type: none"> Tissue-engineered products: the reconstruction, repair, or formation of the structure or function of the human (or animal) body Cellular therapy products: the treatment or prevention of human (or animal) diseases Gene therapy products: intended for the treatment of diseases in humans (or animals) and transfected to human (or animal) cells 	21 CFR 1271.10(a)
Japan	Regenerative medicinal product	<ul style="list-style-type: none"> Processed human or animal cells intended for either: <ul style="list-style-type: none"> Tissue-engineered products: the reconstruction, repair, or formation of the structure or function of the human (or animal) body Cellular therapy products: the treatment or prevention of human (or animal) diseases Gene therapy products: intended for the treatment of diseases in humans (or animals) and transfected to human (or animal) cells 	PMD Act Chapter 1, Article 2, paragraph 2
Australia	Biologicals	<ul style="list-style-type: none"> An entity that either comprises, contains, or is derived from human cells or human tissues and is likely to be used: <ul style="list-style-type: none"> in the treatment or prevention of a disease, ailment, defect, or injury affecting persons, in making a medical diagnosis of the condition of a person, in influencing, inhibiting, or modifying a physiological process in persons, in testing the susceptibility of persons to a disease or ailment, or—in the replacement or modification of parts of a person's anatomy 	Therapeutic Goods Act 1989 Part3-2A-Biologicals 32A
	Autologous human cell and tissue products	<ul style="list-style-type: none"> Those that comprise, contain, or are derived from human cells and tissues Those that are removed from, and applied to, the same person 	ARGB
Korea	ATMPs	<ul style="list-style-type: none"> Cell therapy products: pharmaceuticals manufactured through manipulation of live human or animal cells by physical, chemical, or biological methods, such as <i>in vitro</i> culture, propagation, or selection 	Act on the Safety and Support of Advanced Regenerative Medicine and Advanced Therapy Medicinal Products, Article 2

EU, European Union; US, United States; EC, European Commission; CFR, Code of Federal Regulations; PMD, Pharmaceuticals and Medical Devices.

3.6. Clinical trials of autologous chondrocyte products for articular cartilage repair

We examined the clinical status of ACs on the [ClinicalTrials.gov](https://clinicaltrials.gov) site (as of October 7, 2021), and our results revealed that 62 clinical trials had been conducted or completed. Excluding 16 clinical trials not related to ACI (related to surgery: NCT03137914, NCT04889443, NCT02037204, NCT02738476, NCT04785092, NCT01041885, and NCT03013049; oral ANGPTL3 agonist:

NCT03334812; stem cell therapy: NCT01399749, NCT05016011, NCT03909139, NCT00885729, NCT04953572, and NCT02351011; platelet-rich plasma: NCT03164122 and NCT02964143), a total of 46 clinical trials were summarized by lesion, product name, country or area, registration year, study phase, sample size, study sponsor, and study status (Table 6, Fig. 6). Unclear application area was classified as “Others” (Table 6).

By lesion, the knee was the most frequent, accounting for 37 out of 46 cases (80%), followed by the ankle and hip (2 cases) and then

Table 6
Clinical trials of the safety and/or efficacy of autologous chondrocyte products.

Lesion	Product	Country or area	Registration year	Research Phase	Sample size	Research Sponsor	Study status	Trial Identifier
Knee	ACI	EU	2007	III	58	Hospital	Completed	NCT00560664
			2011	NA	80	Hospital	Active, not recruiting	NCT01458782
			2015	NA	82	Hospital	Recruiting	NCT02636881
			2017	NA	100	Hospital	Recruiting	NCT04296487
	ChondroCelect®	EU	2006	III	118	TiGenix n.v.	Completed	NCT00414700
			2008	III	144	Vericel Corporation	Completed	NCT00719576
	MACI®	EU	2010	IV	128	Vericel Corporation	Completed	NCT01251588
			2009	III	40	Histogenics Corporation	Terminated	NCT00945399
	CARTIPATCH®	EU	2010	II	73	co.don AG	Completed	NCT01225575
			2010	III	102	co.don AG	Completed	NCT01222559
	TEP	EU	2012	I	18	Yan Jin	Completed	NCT01605201
	TEP	EU	2016	II	108	Hospital	Active, not recruiting	NCT02673905
	NOVOCART® 3D plus	NA	2012	III	263	Tetec AG	Active, not recruiting	NCT01656902
			2017	III	30	Aesculap Biologics	Unknown	NCT03219307
	NOVOCART® 3D	US	2013	III	233	Aesculap Biologics	Recruiting	NCT01957722
			2016	IV	245	Tetec AG	Completed	NCT02941120
	NOVOCART®	EU	2019	IV	42	Tetec AG	Active, not recruiting	NCT04186208
			2015	IV	81	Tetec AG	Completed	NCT02348697
	NOVOCART® Inject plus	NA	2017	III	100	Tetec AG	Active, not recruiting	NCT03319797
	A mixture of allogenic MSCs and autologous chondrons with a fibrin cell carrier (Tisseel®)	EU	2020	III	60	Biosolution Co., Ltd.	Recruiting	NCT04236739
	Chondron®	Korea	2010	IV	127	Sewon Cellontech Co., Ltd.	Completed	NCT01056900
			2015	IV	24	Sewon Cellontech Co., Ltd.	Unknown	NCT02539056
			2015	IV	10	Sewon Cellontech Co., Ltd.	Unknown	NCT02539069
			2015	IV	50	Sewon Cellontech Co., Ltd.	Unknown	NCT02524509
			2018	I	6	Biosolution Co., Ltd.	Completed	NCT03517046
	Cartilife®	Korea	2018	II	30	Biosolution Co., Ltd.	Completed	NCT03545269
			2021	III	104	Biosolution Co., Ltd.	Recruiting	NCT05051332
			2021	II	50	Sewon Cellontech Co., Ltd.	Recruiting	NCT04744402
	Carticel®	US	2005	IV	126	Vericel Corporation	Completed	NCT00158613
			2005	IV	2233	Orthopaedic Research Foundation	Completed	NCT00140634
			2005	IV	35	TBF Genie Tissulaire	Completed	NCT00212849
	NeoCart®	US	2010	III	245	Hospital	Terminated	NCT01066702
	Allogeneic culture-expanded adipose-derived MSCs combined with autologous cartilage cells	US	2018	I	25	Hospital	Recruiting	NCT03672825
A mixture of allogenic MSCs and autologous chondrons with a fibrin cell carrier (Tisseel®)	EU	2020	III	60	Biosolution Co., Ltd.	Recruiting	NCT04236739	
BioCart™II	US, Israel	2008	II	40	Hospital	Unknown	NCT00729716	
		2012	I, II	10	Hospital	Completed	NCT01503970	
		2013	III	48	Hospital	Completed	NCT01947374	
		2011	NA	10	Hospital	Unknown	NCT01409447	
		2010	III	30	Sewon Cellontech Co., Ltd.	Completed	NCT01050816	
Ankle	Korea	2015	III	28	ProChon Biotech, Ltd.	Unknown	NCT02537067	
		2010	III	30	Sewon Cellontech Co., Ltd.	Completed	NCT01050816	
Alar lobule	TEP	EU	2010	I	5	Royan Institute	Completed	NCT01242618
Hip	ACI	Iran	2011	I	6	Hospital	Completed	NCT01500811
			2014	IV	21	Tetec AG	Completed	NCT02179346
Lumbar	NOVOCART® Disc plus	EU	2012	I, II	120	Tetec AG	Completed	NCT01640457
Nasal septum	TEP	EU	2020	I	5	Hospital	Recruiting	NCT04633928
Others	CS-ACI	China	2012	I, II	10	Hospital	Unknown	NCT01694823
			2016	NA	100	Hospital	Unknown	NCT02770209

US, United States; EU, European Union; NA, not applicable; ACI, autologous chondrocyte implantation; AMECI, arthroscopic matrix-encapsulated chondrocyte implantation; TEP, tissue-engineered product; MSCs, mesenchymal stem cells; CS-ACI, cell sheet-autologous chondrocyte implantation.

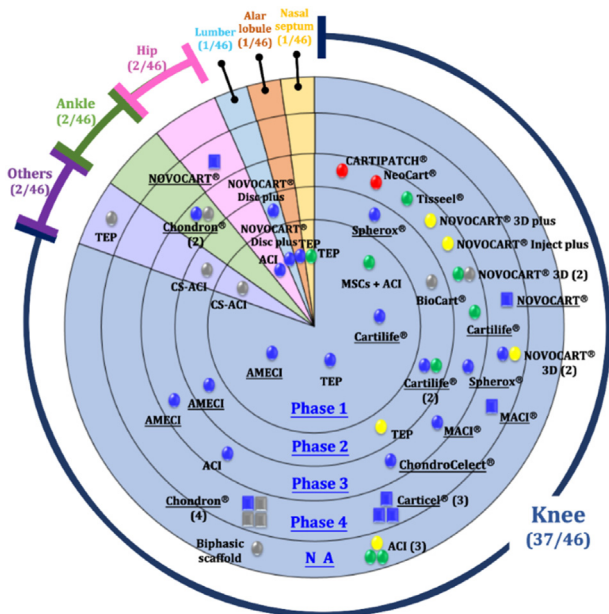


Fig. 6. Clinical trials evaluating the safety and/or efficacy of autologous chondrocyte products. NA, not applicable; ACI, autologous chondrocyte implantation; AMECI, arthroscopic matrix encapsulated chondrocyte implantation; TEP, tissue-engineered product; MSCs, mesenchymal stem cells; CS-ACI, cell sheet-autologous chondrocyte implantation.

the lumber, alar lobule, and nasal septum (1 case each). Among countries where clinical trials were conducted, Europe had the largest number of cases (19, 41%), followed by Korea (9, 20%), the US (8, 17%), China and Mexico (2 cases each, 4%), and Israel, Iran, and Taiwan (1 case each, 2%).

A study showed that cartilage cells were collected using tissue engineering agents to treat other defects, such as engineered nasal cartilage grafts for traumatic injuries of the knee (NCT01605201). There has also been a study on the combination of ACI and stem cell therapy (NCT04236739). ACI is a costly procedure because of the cell culturing process; however, the addition of MSCs enhances cartilage regeneration. The combination of ACI and stem cell therapy further increases cartilage matrix formation, allowing a one-stage application compared with the two-stage ACI procedure [33].

Most of the companies conducting clinical research were biopharmaceutical companies, but medical institutions have also performed numerous studies. Observational studies are also underway to confirm the long-term safety of the approved products.

Compared to AC treatments, allogeneic chondrocyte treatments are associated with a risk of immunological rejection and infectious disease transmission [34]. After searching the ClinicalTrials.gov site (as of October 7, 2021), we identified a total of 11 clinical trials, of which 7 explored the efficacy of allogeneic chondrocytes for degenerative arthritis, not for cartilage defects, and 3 examined combination treatments AC and allogenic chondrocytes.

4. Discussion

This study investigated the status and characteristics of globally approved ACs. Regulations for pre- and post-approved ACs were compared. Subsequently, the technological evolution of AC products is reviewed and regulations related to AC products are compared. The status of AC clinical trials has also been investigated.

Eight products have been approved in the last 20 years since the first guidelines for Manipulated Autologous Structural (MAS) cells were published in the US on May 28, 1996 [35] and since the first AC

Carticel® was approved by the FDA on August 22, 1997. Among these products, the license for ChondroCelect® was withdrawn by TiGenix N.V. in 2016 for commercial reasons [36]. MACI® was first approved in Europe after Vericel Corporation acquired the cell therapy and regulatory media business of Genzyme, but the plant was closed in September 2014 because of low sales [37]. Since then, MACI® entered the US market and was approved by the FDA in December 2016. Chondron® and Cartilage® were reauthorized on August 26, 2021, following the enforcement of the Advanced Regenerative Medicine and Advanced Biopharmaceutical Safety and Support Act in Korea in August 2020.

The effect of cartilage defect treatment was evaluated based on the degree of function and pain improvements. Most of the approved products were investigated based on both patient-subjective evaluation and structural analysis using MRI. Guidelines for nonclinical and clinical approval studies of AC products for knee cartilage repair were published in April 2010 [38] and December 2011 [39] by the EMA and FDA, respectively. Nonclinical tests were conducted to evaluate the pharmacological action and toxicity of AC products. Goats, sheep, and horses were the most frequently used large animal models for cartilage repair studies. Related to the non-clinical study of AC, the literature review and comparative analysis of non-clinical assessment design of AC products by country was published in 2015 [40].

Exploratory clinical trials were performed to examine the dose–response relationships of a product. MF, which is currently recognized as an effective surgical therapy, is recommended as an active control in phase 3 studies, that generally use a randomized controlled design. Most AC products proved their efficacy with a control group of MFs, and some products were conducted as uncontrolled clinical trials. The situation, which was the first approval without similar treatment in the country, was also considered. Methods such as KOOS, which can evaluate function and pain control improvements as primary endpoints, are recommended. If the primary endpoint is subjective, such as patient-reported outcomes, the results must be verified with an objective structural endpoint, such as MRI, as a co-primary endpoint or a main secondary endpoint [38,39]. The EMA guidelines explain that because MF is used for treating lesions less than 4 cm² in size, when MF is used as a control, it is necessary to adjust the range of lesion size in the patient group. In the case of the lesion sizes >4 cm², other ACI therapies may be considered as a control. For patients with lesion sizes >4 cm², other ACI therapies may be considered as a control. In case of MACI® and Spherox®, subjects with lesion sizes >4 cm² were included. The Committee stated that the efficacy of AC may have been overestimated and, therefore, requested the further investigation of larger lesions. For this reason, subgroup analyses performed KOOS responder rates with a cut-off of 4 cm² were obtained for the previously mentioned primary outcomes [10,11].

There was a difference in the follow-up period of the clinical trials: the EMA recommended 3 years of follow-up, whereas the FDA recommended at least 2 years. Specifically, the FDA guidelines require more than 5 years of follow-up as part of post-marketing surveillance. Regulatory agencies are taking measures to ensure the long-term safety of AC products because studies have shown that most failures (75%) of ACI therapy occurred at a mean follow-up of 2.5 years [41]. Long-term safety varies from country to country, but was observed for an average of 5.3 years of the approved AC products, and Japan had the longest at 7 years. Spherox® designated as an additional monitoring product. In the EU, medicines that are being monitored particularly closely by regulatory authorities are labeled with a black inverted triangle (▼) in the product information. It is aimed at enhancing the reporting of suspected adverse drug reactions as early as possible to further

inform the safe and effective use of these medicines and their benefit–risk profile when used in everyday medical practice [42].

The approval process for ACs was the same as that for existing biopharmaceuticals, with an average processing length of 282.4 days. Korea has the shortest period of 115 days. Japan was unique in that the approval period was not set but aimed to not exceed 12 months. In Korea, an rapporteurs committee comprised of external reviewers, such as clinical doctors, to ensure expertise and shorten the approval review period. With the development of the pharmaceutical industry, the number of products reviewed for approval has increased. However, state-of-the-art ACs require stringent quality control and safety measures at every step of the manufacturing process, such as cell collection, processing, storage, and transportation. To satisfy both rapid approval review and product safety, various systems have been implemented. For example, the Korean regulatory agency operates a system that allows faster review by sending the data in advance according to the developer's schedule, a system that allows faster review (from 115 days to 90 days) by assigning a dedicated reviewer, and a system that approves a product with phase 2 clinical data under the condition that a phase 3 clinical trial is to be conducted after marketing starts. To support this, the expansion of reviewer manpower and the strengthening of professionalism are also required.

For rapid approval of ACs, Approval systems such as the FDA's "Accelerated Approval," EMA's "Conditional Marketing Authorization," and PMDA's "Conditional and Term-Limited Approval" are implemented. However, these systems are generally used for the approval of therapies for serious, life-threatening diseases. Most approved ACs were validated using the same approval procedures as those of biopharmaceuticals.

The MFDS was the only agency that gave conditional approval after a phase 2 clinical trial as a pivotal study. However, as cases of failure to prove safety and efficacy during phase 3 clinical trials occurred repeatedly after conditional approval was granted, the MFDS amended the regulations, stating that CPAC opinions must be mandatory prior to product approval in cases of conditional approval for phase 3 clinical trials. In addition, to prevent misuse of conditional approval, as of January 21, 2022, regulations will be effective to revoke conditional approval if the order of action is not followed or if the conditional approval is obtained through false or fraudulent means. It is considered that the efforts of both regulatory agencies and developers are required to ensure the long-term safety and efficacy of AC products, even after product approval.

Most countries have established different classifications and definitions of ACs (such as cell therapy, gene therapy, and tissue-engineered products) from those of existing biopharmaceuticals. In the case of cartilage cells, which bind to scaffolds made of biomaterials or synthetic materials, if the scaffold corresponds to a medical device, a medical device review should be conducted.

Among AC-related clinical trials registered on [Clinicaltrials.gov](https://clinicaltrials.gov), knee cartilage studies were the most abundant. Recent studies have employed cartilage cells collected via tissue engineering to treat other defects, such as septum perforation. Moreover, the number of studies on combinations of ACI and stem cell therapy has increased.

In the case of Cartilife®, a phase 3 clinical trial is underway to confirm its extensive safety and efficacy after conditional approval. Phase 2 clinical trials are also underway in the US for FDA approval. In the case of Chondron®, two phase 3 clinical trials have been conducted to expand the indication to ankle cartilage defects. In the NCT01050816 clinical study, American Orthopedic Foot and Ankle Score (AOFAS) was identified as the primary outcome, and ICRS was identified as the primary outcome in the NCT02537067 study.

It was also confirmed that phase 3 clinical trials have been terminated for several products owing to difficulties in proving the long-term safety and efficacy as well as in fundraising.

The limitation of this study is the low number of approved products, which made comprehensive comparative analysis of the products difficult. In addition, GMP- and quality-related reviews at the time of approval were not included in this study. The main adverse reaction reported for related AC products was post-treatment hematoma. Rather than being an adverse reaction to the drug itself, this was a side effect of the procedure due to postoperative adhesions. However, safety issues remain because a significant proportion of the population was not satisfied the long-term follow up period.

According to recent clinical studies, stem cells and a combination of ACs and allogenic chondrocytes are being actively studied as new treatments for cartilage defects.

5. Conclusions

With this study, it was possible to determine the review direction to which regulatory agencies were interested in reviewing AC products for approval such as efficacy endpoints and long-term safety.

In addition, regulatory agencies have implemented various systems to support the development of advanced biopharmaceutical products, and they will amend and supplement the systems when problems arise. Recently, Novel therapies of cartilage defects have been developing such as combination of ACI. We expect that AC products will be used for the treatment of cartilage defect diseases. We also expect this study provide a new perspective to developers by reviewing the development process of AC products and key reviews during the licensing review of regulatory agencies, and by reviewing the current status of clinical trials.

Declaration of competing interest

None.

Acknowledgements

This work was supported by a grant from the Korean government, South Korea (Ministry of Science and ICT, MICT; NRF-2021R1F1A1062044), and by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, South Korea (Grant Number 2021R1A6A1A03044296). The funder had no role in the trial design, data collection, data interpretation, or report preparation. The authors report no conflicts of interest relevant to the published work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.reth.2022.04.004>.

References

- [1] EvaluatePharma. *World Preview. 2019. Outlook to 2024*.
- [2] Yano K, Watanabe N, Tsuyuki K, Ikawa T, Kasanuki H, Yamato M. Regulatory approval for autologous human cells and tissue products in the United States, the European Union, and Japan. *Regen Ther* 2015;1:45–56. <https://doi.org/10.1016/j.reth.2014.10.001>.
- [3] Sellards RA, Nho SJ, Cole BJ. Chondral injuries. *Curr Opin Rheumatol* 2002;14:134–41. <https://doi.org/10.1097/00002281-200203000-00010>.
- [4] Korean Knee Society home page. Available from: <http://www.koreaknee.or.kr/general/event/event01.html>.
- [5] The Committee for Advanced Therapies. (CAT) and the CAT scientific secretariat. *Challenges with advanced therapy medicinal products and how to meet them*. *Nat Rev* 2010;9.
- [6] Alkaya D, Gurcan C, Kilic P, Yilmazer A, Gunhan Gurman. Where is human-based cellular pharmaceutical R&D taking us in cartilage regeneration? 3

- Biotech, vol. 10. Biotech Publishing; 2020. p. 161. <https://doi.org/10.1007/s13205-020-2134-5>.
- [7] Negoro T, Takagaki Y, Okura H, Matsuyama A. Trends in clinical trials for articular cartilage repair by cell therapy. *NPJ Regen Med* 2018;3:17. <https://doi.org/10.1038/s41536-018-0055-2>.
- [8] Oberweis CV, Marchal JA, López-Ruiz E, Gálvez-Martín P. A worldwide overview of regulatory frameworks for tissue-based products. *termis* 2020. *Tissue Eng Part B Rev* 2020;26:181–96. <https://doi.org/10.1089/ten.TEB.2019.0315>.
- [9] European Medicines Agency. Human medicines/European public assessment reports for ChondroCelect® 2009. Available from: URL, <https://www.ema.europa.eu/en/medicines/human/EPAR/chondrocelect>.
- [10] European Medicines Agency. Human medicines/European public assessment reports for MACI®. April 25, 2013. Available from: URL, <https://www.ema.europa.eu/en/medicines/human/EPAR/maci>.
- [11] European Medicines Agency. Human medicines/European public assessment reports for spherex®. 2017. May 18. Available from: URL, <https://www.ema.europa.eu/en/medicines/human/EPAR/spherex>.
- [12] Food and Drug Administration home page. Available from: URL, <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>.
- [13] Pharmaceutical and medical device agency. Review reports: regenerative medical products for JACC®. Available from: URL, <https://www.pmda.go.jp/english/review-services/reviews/approved-information/0004.html>.
- [14] Therapeutic Goods Administration. ARTG for Chondrocytes. Chondrocytes –T-Ortho-ACI. Available from: URL, https://search.tga.gov.au/s/search.html?collection=tgaartg&profile=record&meta_i=289402.
- [15] Ministry of Food and Drug Safety home page. Available from: URL, <https://nedrug.mfds.go.kr/pbp/CCBBB01/getProductDetail?productSeq=202106181>.
- [16] Ministry of Food and Drug Safety home page. Available from: URL, <https://nedrug.mfds.go.kr/pbp/CCBBB01/getProductDetail?productSeq=202105509>.
- [17] Ministry of Food and Drug Safety. Approval review report for Condron®. Available from: URL, <https://nedrug.mfds.go.kr/pbp/CCBAC02/getProduct?totalPages=357&limit=10&searchYn=true&page=1&title=%EC%BD%98%EB%93%9C%EB%A1%A0&jdgmResultInfoSeq=20210000177>.
- [18] Ministry of Food and Drug Safety. Approval review report for Cartilife®. Available from: URL, <https://nedrug.mfds.go.kr/pbp/CCBAC02/getItem?totalPages=1&limit=10&searchYn=true&page=1&title=%EC%B9%B4%ED%8B%B0%EB%9D%BC%EC%9D%B4%ED%94%84&jdgmResultInfoSeq=20210000172>.
- [19] Cline ME, Herman J, Shaw ER, Morton RD. Standardization of the visual analog scale. *Nurs Res* 1992 Nov-Dec;41(6):378–80.
- [20] Insall JN, Dorr LD, Scott RD, Scott WN. Rationale for the knee society clinical rating system. *Clin Orthop Relat Res* 1989 Nov;(248):13–4.
- [21] Basad E, Ishaque B, Bachmann G, Sturz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. *Knee Surg Sports Traumatol Arthrosc*; April 2010. <https://doi.org/10.1007/s00167-009-1028-1>.
- [22] Peterson L, Minas T, Brittberg M, Nilsson A, Sjögren-Jansson E, Lindahl A. Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. *Clin Orthop Relat Res* 2000;374:212–34. <https://doi.org/10.1097/00003086-200005000-00020>.
- [23] Food and Drug Administration. CARTICEL®. Label. 1997.
- [24] Davies RL, Kuiper NJ. Regenerative medicine: a review of the evolution of autologous chondrocyte implantation (ACI) therapy. *Bioengineering* 2019;6:22. <https://doi.org/10.3390/bioengineering6010022>.
- [25] Orthocell Ltd home page, <https://www.orthocell.com.au/cartilage-regeneration>.
- [26] Choi N-Y, Kim B-W, Yeo WJ, Kim H-B, Suh D-S, Kim JS, et al. Gel-type autologous chondrocyte (Chondron™) implantation for treatment of articular cartilage defects of the knee. *BMC Musculoskel Disord* 2010;11:103. <https://doi.org/10.1186/1471-2474-11-103>.
- [27] European Medicines Agency. Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007, vol. 25; 2018. January.
- [28] Food and Drug Administration. PDUFA reauthorization performance goals and procedures fiscal years 2018 through 2022.
- [29] Azuma K. Regulatory landscape of regenerative medicine in Japan. *Curr Stem Cell Rep* 2015;1:118–28. <https://doi.org/10.1007/s40778-015-0012-6>.
- [30] Pharmaceutical and Medical Device Agency. Notice on the standard review timeline for new drug application, 30; 2012. March.
- [31] Ministry of Food and Drug Safety. Understanding of drug product approval and review procedures [in Korean].
- [32] Therapeutic Goods Administration. Autologous human cells and tissues products regulation, Australian Regulatory Guidelines for Biologicals (ARGB). July 2019. Available from: URL, <https://www.tga.gov.au/autologous-human-cells-and-tissues-products-regulation>.
- [33] Korpershoek JV, Vonk LA, Kester EC, Creemers LB, de Windt TS, Kip MMA, et al. Efficacy of one-stage cartilage repair using allogenic mesenchymal stromal cells and autologous chondron transplantation (IMPACT) compared to nonsurgical treatment for focal articular cartilage lesions of the knee: study protocol for a crossover randomized controlled trial. *BMC (Biomed Chromatogr)* 2020;21:842. <https://doi.org/10.1186/s13063-020-04771-8>.
- [34] Kawabe N, Yoshinao M. The repair of full-thickness articular cartilage defects: immune responses to reparative tissue formed by allogenic growth plate chondrocyte implants. *Clin Orthop* July 1991;(268):279–93.
- [35] Food and Drug Administration. Guidance on applications for products comprised of living autologous cells manipulated ex vivo and intended for structural repair or reconstruction, 28; 1996. Availability. May.
- [36] European Medicines Agency. Public statement ChondroCelect® withdrawal marketing authorisation, 13; 2016. September.
- [37] European Medicines Agency. Procedure closure EU manufacturing site. 2014. Available from: URL, <https://www.ema.europa.eu/en/medicines/human/referrals/maci>.
- [38] European Medicines Agency. Reflection paper vitro-cultured chondrocyte containing products cartilage repair knee. April 2010.
- [39] Food and Drug Administration. Guidance for industry: preparation of IDEs and INDs for products intended to repair or replace knee cartilage. December 2011.
- [40] Ikawa T, Yano K, Watanabe N, Masamune K, Yamato M. Non-clinical assessment design of autologous chondrocyte implantation products. *Regen Ther* 2015;1:98–108. <https://doi.org/10.1016/j.reth.2015.06.003>.
- [41] Bruce Moseley Jr J, Anderson Allen F, Browne Jon E, Mandelbaum Bert R, Micheli Lyle J, Freddie Fu, et al. Long-term durability of autologous chondrocyte implantation. *Am J Sports Med* 2010;38(2). <https://doi.org/10.1177/0363546509348000>.
- [42] EMA Medicines under additional monitoring. Available from: URL: <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/medicines-under-additional-monitoring#what-the-black-triangle-means-section>.