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Diverse Approval Systems for Autologous Human Cells and Tissue Products

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Abstract

Human cells and tissue products are newly categorized products which are containing, consisting of, or derived from cells or tissue that are intended for implantation, transplantation, infusion, or transfer into human recipient. The human cells and tissue products are divided as autologous or allogeneic based on their origin. Since another product fabricated with patient's own limbal epithelial stem cells, was approved as conditional approval for therapeutic indication which is the treatment of adult patients with moderate to severe limbal stem cell deficiency in the European Union, we reviewed the European Public Assessment Report. Of the ten autologous human cells and tissue products, the five products were evaluated using the clinical data with clinical experiences as well as retrospective observatory study or registry, or open clinical trials with small subjects, although for the rest of the products comparative clinical trials with control treatment were performed. In general, autologous human cells and tissue products would need post market-oriented evaluation rather than premarket-oriented evaluation for patients because some of these indications are for orphan diseases or life-threatening disease. However, the other products intended for repair of cartilaginous defects of knee, treatment of prostate cancer, or improvement of the appearance of nasolabial fold winkles were evaluated using comparative clinical data. As for the approval pathways, expedited or normal, both approval pathways are available in the US, the EU, and Japan. The expedited pathways include accelerated approval and humanitarian device exception in the US, conditional market authorization and market authorization under exceptional circumstances in the EU, and a conditional/time-limited approval system in Japan. Our additional review suggests that autologous human cells and tissue products approved using the expedited approval pathway would need post market-oriented evaluation rather than premarket-oriented evaluation.

Keywords: Regenerative medicine products; HCT/Ps; ATMPs; Accelerated approval; BLA; Conditional market authorization; Market authorization; Conditional/time-limited approval system; HDE; PMA

Abbreviations:

ATMPs: Advanced Therapy Medicinal Products; BLA: Biologics License Application; CE Marking: Communauté Européenne (European communication) Marking; HCT/Ps: Human Cells, Tissue, and Cellular and Tissue-based Products; HDE: Humanitarian Device Exemption; PMA: Premarket Application

Introduction

Tissue engineering and regenerative medicine are new therapies to be intended to treat acute and chronic disorders, and are expected to enable the regeneration of tissue specific functions [1]. Because human cells and tissue products are derived from human cells and tissues, the products are newly categorized products which are containing, consisting of, or derived from cells or tissue that are intended for implantation, transplantation, infusion, or transfer into human recipient [2]. The human cells and tissue products are divided as autologous or allogeneic based on their origin [3]. Although autologous human cells and tissue products use own cell source without communicable disease infection from other patients, allogeneic human cells and tissue products use cell source from cell bank which have a hazard to be infected by a communicable disease from other patients. So, allogeneic human cells and tissue products need restrict quality control during processing. Regulation and premarket approval system between autologous and allogeneic human cells and tissue products differ [4,5]. Recently, human cells and tissue products have been regulated as human cells, tissues, and cellular and tissue-based products (HCT/Ps) in the United States [2], gene therapy medicinal product, somatic cell therapy medicinal product, and tissue engineered product of advanced therapy medicinal products (ATMPs) in the European Union [3], tissue-engineered product, cellular therapy product, and gene therapy product of regenerative medicine products in Japan [6]. However, few studies have been reported to the definition, category and premarket authorization of human cells and tissue products among three regulatory authorities. [4]. Since another product fabricated with patient's own limbal epithelial stem cells, was approved as conditional approval for therapeutic indication which is the treatment of adult patients with moderate to severe limbal stem cell deficiency in the EU, we reviewed the European Public Assessment Report [7].

Regulation of Human Cells and Tissue Products

Human cells and tissue products have been classified and defined as HCT/Ps in the US, as ATMPs in the EU, and as regenerative medicine products in Japan. In the US, HCT/Ps have been regulated under sections 351 and 361 of the Public Human Service (PHS) Act (42 the

United States Code, 42USC) according to Title 21, Part 1271 in the Code of Federal Regulation (21CFR1271) since May 25, 2005 [2]. In the EU, ATMPs have been regulated under Regulation (EC) No 1394/2007 of the European Parliament and Council of 13 November, 2007 [3]. In Japan, regenerative medicine products have been regulated under Pharmaceuticals and Medical Device (PMD) Act that is same law as the Amended Pharmaceutical Affairs Law (PAL), which was enacted on November 27, 2013 and the effective date was November 27, 2014 [6]. These products had been classified as drugs (biologics) or medical devices according to the primary mode of action [8] before regulating as HCT/Ps, ATMPs, or regenerative medicine products in the US, the EU, and Japan, respectively.

Categorized medical products

Understanding the categorization of medical products needs to elucidate the regulatory framework or legislation of the US, the EU and Japan (Figure1). In the US, the Federal Food, Drug, and Cosmetic (FD&C) Act of 1938 were defined drugs and medical devices and authorized the Food and Drug Administration (FDA) to demand evidence of safety for new drugs [9]. Then, the Medical Device Amendments of 1976 was established the medical device classification (Class I, II, and III) and applied safety and effectiveness safeguards to new medical devices [9]. The PHS Act of 1944 [10] was applied to the HCT/Ps under the sections 351 and 361 as of May 25, 2005, and the HCT/Ps under the section 351 needed premarket approval of the FDA before on the market.

In the EU, Directive 2001/83/EC of the European Parliament and the Council of 6 of November 2001 on the Community Code Relating to Medicinal Products for Human use gave authority to regulate medicinal products (drugs) [11]. After issuing the Regulation (EC) 726/2004 of medicinal products for human use on EU-wide marketing authorization [12], Regulation (EC) No 1394/2007 of the European Parliament and the Council of November 2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) No 726/2004 gave the European Medicinal Agency (EMA) authority to regulate the ATMPs [3]. Otherwise, in the EU, medical devices were controlled under the Council Directive 93/42/EEC of 14 June 1993 Concerning Medical Devices which was a new approach to technical harmonization and standardization for the design and manufacture of medical devices. The medical devices required affixing the CE Marking on the products which meet the essential requirements and declare by the Notified Body instead of authority.

In Japan, the PAL of 1960 has regulated drugs, medical devices, quasi-drugs, and cosmetics [13]. In 2003, it was revised to consider products derived from biological ingredients by introducing a biological product category, but these products were still categorized either drugs or medical device [14]. The Amended PAL, or PMD Act of 2013 were enacted and become law in 2014, which established a new category of regenerative medicine products [6]. After publishing our shared article [4], in Japan the regulatory framework of medical products has changed to establish a new category of regenerative medicine products and to introduce a conditional/time-limited authorization system of regenerative medicinal products [6].

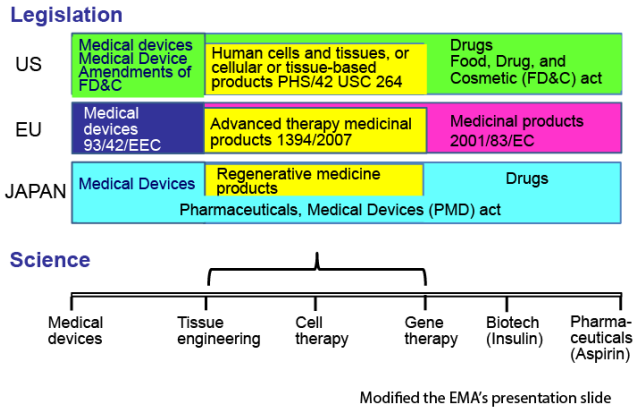

Figure 1: Legislation and science for human cells and tissue products, drugs, and medical devices in the US, the EU, and Japan.In the US, the Federal Food, Drug, and Cosmetic (FD&C) Act of 1938 were defined drugs and medical devices. Then, the Medical Device Amendments of 1976 was established the medical device classification (Class I, II, and III). The PHS Act of 1944 was applied to the human cells and tissue, or cellular or tissue-based products (HCT/Ps) under the sections 351 and 361 as of May 25, 2005, and the HCT/Ps under the section 351 needed premarket approvals of the Food and Drug Administration before on the market. In the EU, Directive 2001/83/EC of the European Parliament and the Council of 6 of November 2001 on the Community Code Relating to Medicinal Products for Human Use gave authority to regulate medicinal products (drugs). After issuing the Regulation (EC) 726/2004 of medicinal products for human use on EU-wide marketing authorization (this regulation is not shown in the figure), Regulation (EC) No 1394/2007 of the European Parliament and the Council of November 2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) No 726/2004 gave the European Medicinal Agency (EMA) authority to regulate the ATMPs. Otherwise, in the EU, medical devices were controlled under the Council Directive 93/42/EEC of 14 June 1993 Concerning Medical Devices. The medical devices required affixing the CE Marking on the products. In Japan, the Pharmaceutical Affairs Law (PAL) of 1960 has regulated drugs, medical devices, quasi-drugs, and cosmetics. The amended PAL, or Pharmaceuticals and Medical Devices (PMD) Act of 2013 were enacted and become law in 2014, which established a new category of regenerative medicine products.

Approval system of autologous human cells and tissue products

Of the ten autologous human cells and tissue products, the nine products were approved by October 2013 [4], and currently another product fabricated with patient's own limbal epithelial stem cells was approved as conditional approval for therapeutic indication which is the treatment of adult patients with moderate to severe limbal stem cell deficiency [7] (Table 1 and Figure 2).

Ten autologous human cells and tissue products were divided into the five groups according to cell origin: chondrocytes, epidermal cells, mononuclear cells, fibroblasts and limbal stem cells. The chondrocytes-derived products which were intended to use as repair of cartilaginous

defects of the femoral condyle or knee joint were CarticelTM [15] in the US, ChonroCelect® [16] and MACI [17] in EU and JACC [18] in Japan. The epidermal cells-derived products which were intended to use as deep dermal or full thickness burns were Epicel® [19] and JACE [20] in the US and Japan respectively. The mononuclear cells-derived products which intended to treatment of asymptomatic or minimally symptomatic metastatic hormone refractory prostate cancer were Provenge® in the US [21] and EU [22]. The fibroblasts-derived product which was intended to improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults was Laviv® [23] in the US. The limbal epithelial stem cells-derived product intended to treatment of adult patients with moderate to severe limbal stem cell deficiency was Holoclar [7] in the EU (Table 1).

Cell origin/ Trade name	Approval date	Approval system	Category	Authority	Intended to use	Pivotal study	Post approval activity
Chondrocytes Carticel™	August 22, 1997	Accelerated approval	HCT/Ps (Biologics)	FDA /CBER	Repair of cartilaginous defects of the femoral condyle	Swedish clinical Experience (153 patients) and US registry	Registry-based study and Follow up study
Chondrocytes ChondroCelect®	October 5, 2009	Market authorization	ATMPs (Drugs)	EMEA/ CHMP	Repair of cartilaginous defects of the femoral condyle	RCT (144 patients)	Pharmacovigilane
Chondrocytes JACC	July 27, 2012	Marketing approval of medical device	Medical devices (Regenerative medicine products)	MHLWPMDA/ OB	Implantation in traumaticcartilage deficiency and Osteochondritis dissecans in the knee joints	Open clinical trial (32 patients)	Post-market survey
Chondrocytes MACI	June 27, 2013	Market authorizations	ATMPs (Drugs)	EMEA /CHMP	Repair of cartilage defects of the knee	RCT (144 patients)	Pharmacovigilane
Epidermal cells Epicel®	October 25, 2007	Humanitarian device exemption (HDE)	Medical devices	FDA/ CDRH	Deep dermal or full thickness burns with greater than or equal to 30% of total surface area	Physician-sponsored study (44 patients)	Not conducted
JACE	October 29, 2007	Marketing approval of medical device	Medical devices (Regenerative medicine products)	MHLWPMDA/ OB	Deep dermal or full thickness burns with greater than or equal to 30% of total surface area	Open clinical trial (2 patients)	Post-approval clinical trial
Mononuclear cells Provenge®	April 29, 2010	Biologics license application (BLA) approval	HCT/Ps (Biologics)	FDA /CBER	Treatment of asymptomatic or minimally symptomatic metastatic hormone refractory prostate cancer	RCT (512 patients)	Registry (1500 patients)
Mononuclear cells Provenge	September 6, 2013	Market authorization	ATMPs (Drugs)	EMEA /CHMP	Treatment of asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer	RCT (512 patients)	Registry (1,500 patients)
Fibroblasts Laviv®	June 21, 2011	Biologics license application (BLA) approval	HCT/Ps (Biologics)	FDA /CBER	Improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults.	Two RCTs (421 patients)	Pharmacovigilance (2,700 patients)
Limbal stem cells Holoclar	February 17, 2015	Conditional marketing	ATMPs (Drugs)	EMEA /CHMP	Treatment of adult patients with moderate to severe limb stem cell deficiency	Retrospective observational	Prospective interventional study

		authorization				study (106 patients)	

Table 1: Approved autologous human cells and tissue products by cell origin HCT/Ps: Human Cells, Tissue, and Cellular and Tissue-based Products; FDA: Food and Drug Administration; CBER: Center for Biologics Evaluation and Research; US: the United States; AMTPs: Advanced Therapy Medicinal Products; EMEA or EMA: European Medicines Agency; CHMP: Committee for Human Medicinal Products; RCT: Randomized Controlled Trial; MHLW: Ministry of Health: Labour and Welfare; PMDA: Pharmaceuticals Medical Device Administration; OB: Office of Biologics; CDRH: Center for Devices and Radiological Health.

Before submitting premarket application dossier to relevant authorities, the five autologous human cells and tissue products such as Carticel™ [15], Epicel® [19], and Laviv® [23] in the US, and MACI [17] and Holoclar [7] in the EU were on the market (Figure 2). Because Carticel™ [15], Epicel® [19], and Laviv® [23] in the US were provided from cell banks before issuing the first guidance regarding manipulated autologous structural cells on May 28, 1996 [24]. Before implementing the central authorization of ATMPs [3], MACI [17] and Holoclar [7] had been authorized in certain European countries (i.e. Austria, Belgium, Denmark, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Portugal, Spain and the United Kingdom) and Italy, respectively. Of the five autologous human cells and tissue products which were on the market prior to premarket application, the three products such as Carticel™ [15], Epicel® [19], and Holoclar [7] were used the clinical experience data to evaluate the safety and efficacy, and were approved as accelerated approval, humanitarian device exemption, conditional marketing authorization, respectively. The rest of the products, MACI [17] and Laviv® [23] were approved as market authorization of ATMP and biologics license application approval using clinical data of randomized control trials (RCT), although the products had the clinical experience data. Of the other five autologous human cells and tissue products, the two products such as JACC [18] and JACE [20] were approved as marketing approval of medical device using clinical data of open clinical trials under the PAL in Japan. Under the PMD Act, however, both products were transferred from medical devices to regenerative medicinal products [25]. The rest of the products, ChondroCelect® [16], and Provenge® in the US [21] and the EU [22] were approved as the market authorization of ATMP, the biologics license application approval, and the market authorization of ATMP, respectively, using clinical data of RCTs.

Autologous human cells and tissue products in the US, the EU and Japan were approved for market authorization using various kind of premarket application system. The preapproval clinical evaluations were conducted with small population or using clinical experience, while a half of the ten products were approved for market authorization using relatively larger clinical data of RCTs. Based on aforementioned premarket approval of autologous human cells and tissue products, the clinical evaluation of the products would focus on premarket-oriented evaluation [4].

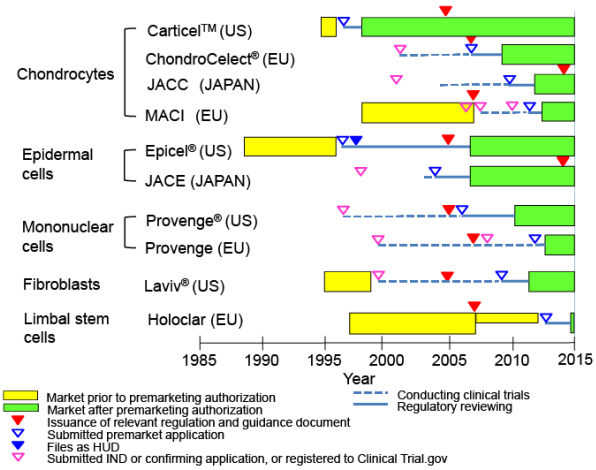

Figure 2: Approved autologous human cells and tissue products in the US, the EU, and Japan of the ten autologous human cells and tissue products, the nine products were approved by October 2013, and currently another product, Holoclar was approved in EU. Before submitting premarket application dossier to relevant authorities, the five autologous human cells and tissue products (yellow bars) in the US, and the EU were on the market. Prior to establishing concrete regulatory framework (red triangles) in the US, and Japan, Epicel®, JACC, and JACE were approved as medical devices.

Expedited or normal approval pathways of autologous human cells and tissue products

Before establishing concrete regulatory framework in the US, and Japan, Epicel® [15], JACC [18], and JACE [20] were approved as medical devices (Table1, Figure 2). As for the approval pathways, expedited or normal, both approval pathways are available in the US, the EU, and Japan (Table 2). The expedited pathways include the accelerated approval and humanitarian device exception in the US, the conditional market authorization and market authorization under exceptional circumstances in the EU, and the conditional/time-limited approval system in Japan (Table 2).

Our additional review suggests that autologous human cells and tissue products approved using the expedited approval pathway would need post market-oriented evaluation rather than premarket-oriented evaluation. Because the autologous human cells and tissue products intended to unmet medical needs or intractable disease, the expedited approval pathway needs to facilitate early clinical application of the products, and to be estimated early on constant updates from limited

number of cased treated [26]. Otherwise, the autologous human cells and tissue products intended to improvement of facial appearance or treatment of cancer need to assess the safety and efficacy during premarket approval. Because there are many patients for treatment of the diseases and it is available to conduct the CRT with control treatment [4]. The strategy of regulatory approval pathway of pharmaceuticals which should use the expedited or normal approval pathway may be same idea for choosing as chemotherapy products such as anticancer drugs and antibiotics.

	Human cells and tissue products	Medical devices
The US		
Expedited pathway	Accelerated approval	Humanitarian device exemption (HDE)
Normal pathway	Biologics license application (BLA) approval as HCT/Ps	Premarket application (PMA) approval
The EU		
Expedited pathway	Conditional market authorization	Manufacturer's declaration of conformity (affixing CE marking)
Normal pathway	Market authorization under exceptional circumstances	Manufacturer's declaration of conformity (affixing CE marking)
(Each EU member)	(Hospital exemption)	(Not exist)
Japan		
Expedited pathway	Conditional and time-limited approval	Orphan medical devices
Normal pathway	Marketing approval of regenerative medicine products	Marketing approval of medical devices

Table 2: Expedited and normal approval pathways of human cells and tissue products and medical devices in the US, the EU and Japan US: Unites State of America; HCT/Ps: Human Cells, Tissue, and Cellular and Tissue-based Products; EU: European Union; AMTPs: Advanced Therapy Medicinal Products; CE: Communauté Européenne (European communication).

Conclusion

Autologous human cells and tissue products in the US, the EU and Japan were approved for market authorization using various kinds of premarket application system. The preapproval clinical evaluations were conducted with small population or using clinical experience, while most of allogeneic human cells and tissue products were approved for market authorization using relatively larger clinical trials. The clinical evaluation of the autologous human cells and tissue products would focus on post market-oriented evaluation to distribute the new products of regenerative medicine, tissue engineering, and cell therapy to patients and to oversee the risk of these products using registry.

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