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Leading opinion

The regulation of allogeneic human cells and tissue products as biomaterials

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ABSTRACT

The current definition of biomaterials differs vastly from it of just a decade ago. According to advancing technologies, it encompasses unpredictable materials such as engineered human cells and tissue. These biomaterials also have to be approved to use in health care business by regulatory authority, which are defined as drug, medical device, or biologics in the regulation. This Leading Opinion Paper addresses the regulatory issues of engineered human cells and tissue products using allogeneic cells that should have a great possibility to develop therapeutics for life-threating diseases or orphan diseases. Six allogeneic human cells and tissue products derived from neonatal or infant fibroblasts and/or keratinocytes were approved as medical devices or biologics in the United States as well as a hematopoietic cell product. For five of the seven products, well-controlled comparative clinical trials were conducted as pre-approval evaluation followed by post-approval evaluation. Although these products avoid a sterilization process usually used for medical devices, no serious malfunction that would lead to class 1 recall was reported. This article would provide insight for development of the engineered human cells and tissue.

1. Introduction

General meaning of words alter with time. Biomaterials was defined as 'a materials intended to interference with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body' in 1999 [1]. With advanced new technology and the scope in the domain of health care, the word of biomaterial has been currently refined as 'a substance that has been engineered to take a form which, alone or part a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure, in human or veterinary medicine.' in 2009 [2]. This Leading Opinion Paper addresses the market approval issue of engineered human cells and tissue products fabricated from allogeneic donor cells, that should have a great possibility to develop therapeutics for life-threating diseases or orphan diseases.

2. Methods

This article included the products comprised of allogeneic human cells approved in the United States (US) until March 2012, since such a product wasn't approved under a current regulation as drugs, medical devices and biologics in the European Union (EU) or Japan. In the US, the human cells, tissue, and cellular and tissue-based products (HCT/Ps) consisted of under sections 351 and 361 of Public Health Service Act (PHS Act; 42 the United State Code) according to the Code of Federal Regulation (CFR), Title 21, Part 1271.20 and 1271.10, respectively. We focused the HCT/Ps under section 351 of PHS Act required premarket approval (PMA) prior to on the market. The HCT/Ps under section 361 was excluded due to no requirement for PMA. The information on the definition and classification of HCT/Ps was obtained from the website of the Food and Drug Administration (FDA) [3]. The information of approved HCT/Ps under the section (biologics license application, BLA), approved medical devices as PMA, humanitarian device exemptions (HDE) was obtained from the appropriate FDA's websites [4,5] and of listing of Center for Devices and Radiological Health (CDRH) HDE [6]. The information of approval review repot for each product was obtained from the appropriate FDA's web sites: Dermagraft-TC™ (currently known as TransCyte®) [7], Apligraf™ [8], Composite Cultured Skin [9], Orcel™ [10], Dermagraft® [11], Hemacord [12], and Gintuit [13]. In the EU and Japan, the information on the definition and classification of advanced therapy medicinal products (ATMPs) and cell/tissue-engineered products were obtained from the website of the European Medicines Agency (EMA) [14], and the Pharmaceuticals and Medical Device Agency (PMDA) [15], respectively. The generic name and trade name, cell origin, approval date, market authorization holder, authority, indication, and category of approved products were obtained from regulatory information [7–13]. History of

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regulatory action, pre-approval and post-approval clinical evaluation were obtained from the appropriate approval review repot or the FDA website [7–13]. Safety information was collected from FDA websites, mainly [16,17].

3. Results

3.1. Major issuances of the legislation for human cell and tissue products

Currently, the engineered human cells and tissue products are regulated as HCT/Ps in the US, ATMPs in the EU, and cell/tissue-engineered products in Japan. These products are also categorized as biologics of medicinal products for human use due to the living sources. Furthermore, the products are classified as drugs or medical devices due to the primary mode of action in the US and Japan [18,19], and divided as autologous and allogeneic based on their origin. Although the definition of human cells and tissue products is comparable among the US, EU, and Japan, it is not exactly equivalent.

In the US, since the first guidance of manipulated autologous cells was issued in 1996 [20], 55 rules or guidance documents for human cells and tissue products were issued. The final rule of establishment registration and listing concerning human cells and tissue products for human use was issued in 2001 [21]. The effective day of the final rule of current good tissue practice (cGTP) for HCT/Ps was on May 25, 2005 [22], and the jurisdiction of the HCT/Ps was transferred from CDRH to the Center for Biologics Evaluation and Research (CBER). Japan has adopted the existing legislation to manage the human cells and tissue products in 2000 [23]. To gain a common European regulatory frameworks, the EU published a new directive and regulation for ATMPs including human cells and tissue products in 2007 [19].

3.2. History of regulatory action, pre-approval and post-approval clinical evaluations of allogeneic human cell and tissue products in the US

The pathways of seven approved allogeneic human cells and tissue products for market authorization in the US were four in PMA, one in HDE, and two in BLA (Table 1, Fig. 1). Six of these seven products were intended for wound covering or dressing of thermal burn wounds and skin ulcers due to venous insufficiency or diabetic vascular complication or surgically created vascular complication. Five of seven products were approved as medical devices, while more recently approved Hemacord and Gintuit were categorized as biologics.

Interactive wound and burn dressing derived from allogeneic fibroblasts with extracellular matrix and bioabsorbable polyglactin mesh scaffold (formerly, Dermagraft-TC™; currently, TransCyte®, Advanced Tissue Science, La Jolla, CA, US), was approved for use as temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in the patients on March 18, 1997 for PMA using one pivotal clinical trial of 66 patients and open study of 11 patients with pilot study of 10 patients and emergency use of only two patients, which were a total of 89 patients. In the pivotal study, the percent take on postautograft day 14 of TransCyte® was superior to control (cadaver skin): 94.7% vs 93.1% ($p = 0.0001$). Post-approval clinical study planned to recruit at least 100 patients for a prospective randomized, comparison study of silver sulfadiazine and TransCyte® was performed with use of paired wound sites on only 14 patients (Table 2). On August 14, 1998, the indication of TransCyte® was expanded to include the treatment of mid-dermal to intermediate depth burn wound that might be expected to heal without autografting [24]. In a randomized, within-patient paired comparison study, the number of days until epithelial closure of at least 90% reepitheliazation for TransCyte® was 11.1 days and 18.1 days for control as topical therapy [25].

Living skin equivalent graftskin derived from allogeneic fibroblasts and keratinocytes with type I bovine collagen (Apligraf™, Organogenesis Inc., Canton, MA, US), was approved for use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than one month duration that had not responded to conventional ulcer therapy on May 22, 1998 using the randomized, controlled clinical trial data of 240 patients (Table 2). In the pivotal study as randomized controlled trial, the incidence of 100% wound closure per unit time of Apligraf™ was statistically significant improvement to control therapy (zinc paste gauge and compression therapy). Post-approval evaluations were additionally conducted to investigate the purity of the transferrin for viral inactivation and karyology of keratinocytes and fibroblasts, and the longevity of Apligraf™ on the patients (Table 2). On June 20, 2000, the indication of Apligraf™ was expanded to include the treatment of diabetic foot ulcers [26]. In a randomized, controlled comparison study with 208 patients (Apligraf™ 112 patients and control 96 patients) for treatment of no infected, no ischemic chronic plantar diabetic foot ulcer, complete wound healing of Apligraf™ was significantly higher than that of control treatment of saline-moistened gauze at the 12-week follow-up visit, 56% (63 patients) and 36% (36 patients), respectively ($p = 0.0042$) [27].

Interactive wound and burn dressing derived from allogeneic epidermal keratinocytes and dermal fibroblasts with bovine type I collagen matrix (Composite Cultured Skin, Ortec International, Inc., New York City, NY, US), was approved under the HDE on February 21, 2001 using clinical study data of 12 patients in the US and Australian clinical study of seven patients for the treatment of Epidermolysis Bullosa, and 74 patients for other diseases after being designated as a humanitarian use device (HUD, 21CFR814.100) that was intended to be benefit for patients by treating a disease affecting fewer than 4000 individuals per year in the US (Table 2). In the randomized, within-patient controlled US study, it was observed no statistically significant differences in the incidence or time to wound healing between the Composite Cultured Skin or standard care including collagen sponge (Table 2).

The same generic name as Interactive wound and burn dressing, but a different trade name (Orcel™, Ortec International, Inc., New York City, NY, US) intended to treat burn wounds, was approved on August 31, 2001 using controlled clinical data of 82 patients after a conducted pilot study with 8 patients (Table 2). In the pivotal study, the time to wound closure (100% reepitheliazation) of Orcel™ was significantly shorter than that of control dressing (Biobrabe-L®) for intend-to-treat (ITT) population ($p = 0.0006$). Post-approval requirements were requested that the methods for evaluating antibody and cellular responses against bovine serum proteins, human blood group, and HLA antigen, as well as a post-approval study evaluating the duration of Orcel™'s cells on the donor site wounds.

Interactive wound dressing derived with allogeneic fibroblasts and biodegradable synthetic polymer, polyglactin, mesh scaffold (Dermagraft®, Advanced Tissue Science, La Jolla, CA, US) was approved for treatment of full-thickness diabetic foot ulcers greater than six weeks duration on March 18, 1997 for PMA using two controlled pivotal trials of 281 patients and 314 patients, and a feasibility study of 50 patients in addition to a supplementary study of 50 patients and treatment IDE of 49 patients (Table 2). In one of the pivotal studies with 314 patient as randomized controlled trial, complete wound closure by 12 weeks of Dermagraft® was significantly improved compared with control therapy (saline-moistened gauze and pressure-reducing footwear): 30.0% (39 of 130 patients) and 18.3% (21 of 115 patients), respectively.