revised and submitted to *Biomaterials as a* Leading Opinion

The Regulation of Allogeneic Human Cells and Tissue Products as Biomaterials

K Yano[1], K Tsuyuki[1], N Watanabe[1,2], H Kasanuki[1] and M Yamato[1,2]*

[1] Cooperative Major in Advanced Biomedical Sciences, Joint Graduate School of Tokyo Women's Medical University and Waseda University, Tokyo, Japan; [2]Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Tokyo, Japan.

*__Correspondence__: Masayuki Yamato, Ph. D., Joint Graduate School of Tokyo Women's Medical University and Waseda University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-866, Japan; E-mail: myamato@abmes.twmu.ac.jp; Fax: +81-3-3359-6046; Tel: +81-3-5367-9945 Ext. 6211.,

Kazuo Yano, D.V.M, Joint Graduate School of Tokyo Women's Medical University and Waseda University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-866, Japan; E-mail: yano.kw@akane.waseda.jp; Fax: +81-3-3359-6046; Tel: +81-3-5367-9945 Ext. 6211.,

Kenichiro Tsuyuki, Joint Graduate School of Tokyo Women's Medical University and Waseda University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-866, Japan; E-mail: ken.tsuyuki@akane.waseda.jp; Fax: +81-3-3359-6046; Tel: +81-3-5367-9945 Ext. 6211.,

Natsumi Watanabe, Ph. D., Joint Graduate School of Tokyo Women's Medical University and Waseda University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-866, Japan; E-mail: nwatanabe@abmes.twmu.ac.jp; Fax: +81-3-3359-6046; Tel: +81-3-5367-9945 Ext. 6223,

Hiroshi Kasanuki, M.D., Ph. D., Joint Graduate School of Tokyo Women's Medical University and Waseda University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-866, Japan; E-mail: hkasanuki@jheart.or.jp; Fax: +81-3-3356-7969; Tel: +81-3-3356-7969.

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.

Keywords: Allogeneic cell, Blood, Epithelium, Fibroblast, Mesenchymal stem cell, Wound dressing

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 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 (**Tables 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.

Umbilical cord blood has been used as source of hematopoietic stem cells for allogeneic hematopoietic stem cell transplant for over 20 years in the US [28]. According to the issuance of the guidance on allogeneic placental/umbilical cord

blood [29], hematopoietic progenitor cells, cord blood, was regulated as human cells and tissue products after October 20, 2011. The products composed of allogeneic cord blood, 10% DMSO, and 1% Dextran 40 in 25 mL total volume (Hemacord, New York Blood Center, Inc., New York, NY, US) was approved on November 10, 2011 using clinical review including published literatures indicated that sufficient evidence of efficacy and safety for treating patients with hematologic malignancy and nonmalignant indications (**Table 2**).

Allogeneic cultured keratinocytes and fibroblasts in bovine type I collagen hydrogel as same products as Apligraf ™ but with differed indication for treatment of mucogingival condition (Gintuit, Organogenesis Inc., Canton, MA, US) was approved on March 9, 2012 using two controlled clinical trials of 25 patients and 96 patients with pilot study of 15 patients (**Table 2**), although PMA dossier of Gintuit had been refused to accept by CDRH due to changing its jurisdiction from CDRH to CBER, and BLA dossier also was submitted to CBER. In the first pivotal study, Gintuit failed to demonstrate non-inferiority to control for the primary efficacy endpoint, however, in the second pivotal study, the primary efficacy endpoint met to compare to a 50% success rate in single-arm comparison and the study found superiority of Gintuit to control in three of the six secondary endpoints.

3.3. Safety information, recalls, and change records of PMA approval

According to the database of manufacturer and user facility device experience (MAUDE), adverse event reports consisted of voluntary reports, user facility report, distributor report, and manufacture report were submitted to the FDA for the following two products: 73 reports for Dermagraft ® which includes Dermagraft-TC™ and TransCyte ® and 13 reports for Apligraf™ which includes Graftskin (**Fig. 2**). Other

safety information such Dear Healthcare Professional Letter has not been found on the appropriate URL on the FDA. Recalls also were voluntarily conducted on the two products, Dermagraft ® and Apligraf™ (**Table 3**). Although recalls information was posted six times for Apligraf™, eight more recalls were reported due to mainly microbial contamination of agarose in 1999 to 2011 according to Chemistry, Manufacturing and Control (CMC) review of Gintuit [30] .

After PMA, any PMA holder has to submit PMA supplement that meets any change that affects or enhances the safety and effectiveness of the device. PMA supplement is divided into three categories, that are PMA supplement for significant change (CFR 814.39(a)), special PMA supplement for labeling change (CFR 814.39 (d)), and 30-day notice and 135-day PMA supplement for modification to manufacturing procedure (CFR 814.39(f)) [31]. PMA supplement was submitted to the FDA in four of seven human cells and tissue products (**Table 4**). It is noteworthy that the PMA holder for Apligraf™ submitted PMA supplement 68 times from 1998 to 2012: it consists of 50 times for manufacture procedure change, seven times for labeling change, one time for post-approval protocol, 10 times for not described information. Furthermore, 21 of 50 for manufacture process change were for introduction of human epidermal keratinocyte or fibroblast cell strains.

4. Discussion

Five of the seven products, Dermagraft-TC™, Dermagraft®, Apligraf™, Composite Cultured Skin, and Orcel™ were evaluated as medical devices in pre-approval evaluation after conducted several non-clinical examinations. Five of them were conducted as pivotal clinical trials with investigation device and comparator such as control treatment to confirm safety and efficacy even serious injury as burn after

conducting pilot or feasibility trials. These pre-market evaluations of pivotal trial comply to medical device's guidance [32]. Clinical trials of Guntuit was started as medical device, however, it was finally submitted as BLA, because of its jurisdiction change after conducting two pivotal studies [33]. These allogeneic human cells and tissue products were approved for market authorization using relatively larger clinical trial than that for autologous products, while more postmarket surveillance was imposed on autologous products [34-36] . Otherwise, Hemacord had been on the market as blood banks for long time before issued related guidance [29], and was submitted as BLA with published references, guidance and own data without non clinical data such as toxicology. This product was applied similar application dossier as autologous human cells and tissue products as Carticel™ [34] and Epicel® [35] which had been used clinical experience data (not clinical trial data), and Laviv® [36] which had used just clinical trial data with non-clinical data. As post-approval clinical trial, multi-center, nonrandomized, unmasked study to receive Dermagraft-TC™ was conducted as condition of approval for at least 100 patients, however, it has actually completed to accumulate 14 patents without narrowing indication. Under the condition of approval, it is different from Carticel™ as autologous human cells and tissues product which was narrowed the indication due to incompletion (suspension) of clinical trial [37].

The cumulative number of patients of Dermagraft® were less than 50000 patients as of 31 March 2010 [38], approximately 450000 patients for Apligraf™ [39]. We calculated that the incident rates of were approximately 0.146% for Dermagraft® and 0.003% for Apligraf™. The incident rate would not be so high as other dressing products. Other safety information, recalls were mostly conducted for Apligraf™ and the amount of recalls are relatively small. There were some common sources of

failure such as microbiological contamination of agarose which is known to be a regent that is particularly susceptible to microbiological contamination, however, the relative frequency was low according to US FDA reviewer's assessment [30]. In addition of low frequency of recall, class I recall which is a situation in which there is reasonable probability that the uses of violate product will cause serious adverse health consequences or death were not conducted. Then, as much as recalls posted on US FDA web of blood products as biologics were not observed. Due to relatively low frequency of AE and relative low of recalls, allogeneic human cells and tissue products will be a safety medicine products.

As submitted as PMA supplement, the sponsor of Apligraf™ submitted 68 PMA supplements: the most of the reasons were the manufacture process changing which was 50 times, because new cell line of fibroblasts and keratinocytes from neonatal foreskin. In the case of TransCyte®, 10 of 21 PMA supplements were the manufacture process changing. The duration of PMA supplements of TransCyte® were mostly normal PMA supplement (180-day), however, Apligraf™ and Dermagraft® were mainly real –time supplement or 30- day/135 -day due to burdensome policy. In accordance with BLA and BLA's supplement, sponsor must submmit any change as "changes being effected: CBEs and CBE-30s" , "prior approval to distribute of product: PAS", and "annual report: AR". Prior PMA supplements as normal PMA supplement will be adequate of PAS of BLA change; the real-time supplement of PMA will be CBEs and CBE-30S of BLA change; administrative change will be AR ([40] Assuring User Fees).

Finally, as indicated in the Table 1, Dermagraft-TC™ was intended to use as temporary coveing for surgically excised full-thicness and deep partial-thickness thermal burn such a covering prior to autograft replacement. Composite Cultured

Skin was intended to use in the patient with mitten hand deformity due to Recessive Dystrophic Epidermolysis Bullosa (RDEB) as adjunct to standard autograft for covering for covering wounds and donor sites created after the surgical release offhand contraction. We suggest allogeneic human cells and tissue products have a great possibility to develop therapeutics for life-threating diseases or orphan diseases.

5. Conclusion

Allogeneic human cells and tissue products were approved for market authorization using larger clinical trial than that for autologous products, while more postmarket surveillance was imposed on autologous products. For allogeneic human cells and tissue products, well-controlled comparative studies were conducted as drugs and medical device. Well-organized issuance of appropriate rules and guidelines would promote the development and approval of human cell and tissue products.

Acknowledgements

This work was supported by the Creation of Innovation Centers for Advanced Interdisciplinary Research Areas Program in the Project for Developing Innovation Systems "Cell Sheet Tissue Engineering Center (CSTEC)" and the Global COE program, the Multidisciplinary Education and Research Center for Regenerative Medicine (MERCREM), from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

References

[1] Williams DF. The Williams dictionary of biomaterials. Liverpool: Liverpool University Press; 1999.

[2] Williams DF. On the nature of biomaterials. Biomaterials 2009;30:5897-909.

[3] US Food and Drug Administration. Vaccines, Blood & Biologics Topics. 2012. Available from URL: http://www.fda.gov/BiologicsBloodVaccines/default.htm

[4] US Food and Drug Administration. Biological Approvals by Year. 2012. Available from URL: http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicalApprovalsbyYear/default.htm

[5] US Food and Drug Administration. PMA Approvals. 2012. Available from URL: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm

[6] US Food and Drug Administration. Listing of CDRH Humanitarian Device Exemptions. 2012. Available from URL: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm

[7] US Food and Drug Administration. Appoval Letter of Dermagraft Temporary Covering , Dermagraft-TC™. 1997. Available from URL: http://www.accessdata.fda.gov/cdrh_docs/pdf/p960007.pdf

[8] US Food and Drug Administration. Apligraf™ (Graftskin) - P950032. 1998. Available from URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=p950032

[9] US Food and Drug Administration. Composite Cultured Skin (CCS) - H990013. 2001. Available from URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H990013

[10] US Food and Drug Administration. OrCel™ Bilayered Cellular Matrix - P010016. 2001. Available from URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=p010016

[11] US Food and Drug Administration. DERMAGRAFT® - P000036. 2001. Available from URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P000036

[12] US Food and Drug Administration. HEMACORD (hematopoietic progenitor cells, cord blood). 2011. Available from URL: http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm279608.htm

[13] US Food and Drug Administration. GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen). 2012. Available from URL: http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm295465.htm

[14] The European Medicines Agency. Home page The European Medicines Agency. 2012. Available from URL: http://www.ema.europa.eu/ema/

[15] The Pharmaceuticals and Medical Devices Agency. Home pages The Pharmaceuticals and Medical Devices Agency 2012. Available from URL: http://www.pmda.go.jp/

[16] US Food and Drug Administration. List of Device Recalls. 2012. Available from URL: http://www.fda.gov/MedicalDevices/Safety/RecallsCorrectionsRemovals/ListofRecalls/default.htm

[17] US Food and Drug Administration. MAUDE - Manufacturer and User Facility Device Exprience. 2012. Available from URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM

[18] US Food and Drug Administration, Department of Health and Human Service. Definition of Primary Mode of Action of a Combination Product. Fed Regist 2005;70:49848-62.

[19] European Parliament and the Council of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinalproducts and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union 2007;L324:121-37.

[20] US Food and Drug Administration. Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated Ex Vivo and Intendeded for StructualRepair or Reconstruction; Availability. Fedral Register 1996;61:26523-4.

[21] US Food and Drug Administration. Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing. Fed Regist 2001;66:5447-69.

[22] US Food and Drug Administration. Current Good Tissue Practice for Human Cells, Tissues,

and Cellular and Tissue-Based Product Establishment; Inspection and Enforcement. Fed Regist 2004;69:68612-88.

[23] Pharmaceutical and Food Safety Bureau. Quality and safety assurance for drug products manufactured using human- or animal-derived components as raw materials, Appendix 1: Basic policies for handling and using drug products using cells and tissue; Appendix 2: Guidance regarding quality and safety assurance for drug products manufactured by processing human-derived cells and tissue (in Japanese). Iyakuhatsu: PFSB notification 2000; 1314.

[24] US Food and Drug Administration. August 1998 PMA Approvals: TransCyte™ P960007/S008. 1998. Available from URL: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/ucm115123.htm

[25] Noordenbos J, Dore C, Hansbrough JF. Safety and efficacy of TransCyte for the treatment of partial-thickness burns. J Burn Care Rehabil 1999;20:275-81.

[26] US Food and Drug Administration. Approval Letter: Apligraf ® (Grafskin) - P950032/S016. 2000. Available from URL: http://www.accessdata.fda.gov/cdrh_docs/pdf/P950032S016a.pdf

[27] Veves A, Falanga V, Armstrong DG, Sabolinski ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. Diabetes Care 2001;24:290-5.

[28] US Food and Drug Administration. Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Bllod Hematopoietic Stem/Progenitor Cell Products; Request for Comments. Fed Regist 1998;63:2985-8.

[29] US Food and Drug Administration. Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications; Avalability. Fed Regist 2009;74:53753-4.

[30] US Food and Drug Administration. CMC Review: BLA125400/0. 2012. Available from URL: http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM297874.pdf

[31] US Food and Drug Administration. CFR - Code of Federal Regulations Title 21, PART 814 --

PREMARKET APPROVAL OF MEDICAL DEVICES, Subpart B--Premarket Approval Application (PMA) , Sec. 814.39 PMA supplements

2012. Available from URL:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=814.39

[32] Kessler L. G. Statistical Guidance for Clinical Trials of Non Diagnostic Medical Devices. 1996. Available from URL:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm106757.htm

[33] US Food and Drug Administration. Summary Basis for Regulatory Action. 2012. Available from URL:

http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM297753.pdf

[34] US Food and Drug Administration. Summary for Basis of Approval - Carticel. 1997. Available from URL:

http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM109341.pdf

[35] US Food and Drug Administration. Epicel® (cultured epidermal autografts) - H990002, Summary of Safety and Probable Benefit. 2007. Available from URL:

http://www.accessdata.fda.gov/cdrh_docs/pdf/H990002b.pdf

[36] US Food and Drug Administration. Summary Basis for Regulatory Action, June 20, 2011 - Laviv 2011. Available from URL:

http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM262780.pdf

[37] US Food and Drug Administration. March 2, 2000 Approval Letter - Carticel. 2000. Available from URL:

http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm163013.htm

[38] Mason C, Manzotti E. Regenerative medicine cell therapies: numbers of units manufactured and patients treated between 1988 and 2010. Regen Med 2010;5:307-13.

[39] Schmidt C. Gintuit cell therapy approval signals shift at US regulator. Nat Biotechnol 2012;30:479.

[40] US Food and Drug Administration. Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products; Guidance for Industry and FDA. 2003. Available from URL: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089730.pdf

Figure Legends

Fig. 1. Pathway of approved allogeneic human cells and tissue products in the US. IND: investigational new drugs; HDE: humanitarian device exemption; HCT/P: human cells, tissue, and cellular and tissue-based products.

After authorized expedited review status in 1995, Apligraf™ was filed as PMA for medical device on October 4, 1995, and approved on May 22, 1998. Formerly Dermagraft-TC™ (currently, TransCyte®) also was filed as premarket application (PMA) on March 16, 1996 and approved on March 18, 1997. Same generic name as interactive wound and burn dressing, but different trade name as Composite Cultured Skin was designated as humanitarian use device (HUD) on December 24, 1998 and approved as HDE on February 21, 2001. Just after approved HDE, the other trade name as Orcel™ was filed as PMA, and approved on August 31, 2001. As extended indication, Dermagraft® which was different trade name of Dermagraft-TC™ was filed as PMA on August 25, 2000, and approved on September 28, 2001. In the US, regulatory impact occurred on human cells and tissue products after May 25, 2005 which was effective of three rules[1-3)] of the HCT/Ps due to changing its jurisdiction from Center for Device and Radiological Health (CDRH) to Center for Biologics Evaluation and Research (CBER). In 2007, additional rule of HCT/Ps was effective on June 19[4)]. As extended indication of Apligraf™, Gintuit was submitted as biologic license application (BLA) after had refused to file as PMA, and approved as biologic products on March 9, 2012. The other regulatory impact was allogeneic placental/umbilical cord bloods that have been used as source of hematopoietic stem cells for allogeneic hematopoietic stem cell transplant for over 20 years in the US. The product also was regulated as HCT/Ps after October 20, 2011. Hemacord was

submitted as BLA on January 10, 2011, and approved on November 10, 2011.

<Reference>

1) US Food and Drug Administration. Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing. Fed Regist 2001;66(13):5447-69, Final Rules January 19.

2) US Food and Drug Administration. Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products. Fed Regist 2004; 69(101):2978629834, Final Rule May 25.

3) US Food and Drug Administration. Current Good Tissue Practice for Human Cells, Tissues, and Cellular and Tissue-Based Product Establishment; Inspection and Enforcement. Fed Regist 2004;69(226):68612-88, Final Rule November 24.

4) US Food and Drug Administration. Human Cells, Tissues, and Cellular and Tissue-Based Products; Donor Screening and Testing, and Related Labeling, Fed Regist 2007;72(117):33667-9, Final rule June 19.

Fig. 2. Adverse event reports of allogeneic human cells and tissue products in the US.

These figures indicate a number of adverse event (AE) reports with regard to both products, Dermagraft® (Left) and Apligraf™ (Right) from 1997 to as of the end of June in 2012. The data sources are the database of manufacturer and user facility device experience (MAUDE: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM). Of seven products, two products, Dermagraft® which includes Dermagraft-TC™ and TransCyte ® was submitted 73 reports; Apligraf™ which includes Graftskin was 13 reports. In Dermagraft®, a lot of AE reports based on AEs mainly microbial infection

and serious AE including death were submitted during for five years after on the market and a current years. Otherwise, in Apligraf™, one or two report was submitted annually.

Table 1 Approved allogeneic human cells and tissue products in the US

Generic name (Trade name)	Cell origin (Material)	Approval date	Marketing authorization holder	Authority	Indication	Category
Interactive wound and burn dressing (Formerly, Dermagraft-TC™, currently, TransCyte®)	Allogeneic fibroblasts (Extracellular matrix and bioabsorbable polyglactin mesh scaffold)	March 18, 1997 (PMA)	Advanced Tissue Science, La Jolla, CA, US (1997-2002)	FDA/ CDRH	Use as temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in patients who require such a covering prior to autograft replacement	Medical device
		August 14, 1998 (PMA/ supplement)	Smith & Nephew, Jolla, CA, US (2002-2005)		Treatment of mid-dermal to indeterminate depth burn wounds not requiring autografting	
			Advanced BioHealing[1)], La Jolla, CA, US (2006-)			
Living Skin Equivalent (LSE) Graftskin (Apligraf™)	Allogeneic fibroblasts and keratinocytes (Type I bovine collagen)	May 22, 1998 (PMA)	Organogenesis Inc., Canton, MA, US	FDA/ CDRH	Use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy.	Medical device
		June 20, 2000 (PMA/ supplement)			Treatment of diabetic foot ulcers	

Table 1 Continued

Generic name (Trade name)	Cell origin (Material)	Approval date	Marketing authorization holder	Authority	Indication	Category
Interactive wound and burn dressing (Composite Cultured Skin)	Allogeneic epidermal keratinocytes and dermal fibroblasts (Bovine collagen matrix)	February 21, 2001 (HDE)	Ortec International, Inc., New York City, NY, US	FDA/ CDRH	Use in patients with mitten hand deformity due to Recessive Dystrophic Epidermolysis Bullosa (RDEB) as adjunct to standard autograft procedure (i.e., skin grafts and flaps) for covering wounds and donor sites created after the surgical release offhand contraction (i.e., mitten hand deformity)	Medical device
Interactive wound and burn dressing (Orcel™)	Allogeneic epidermal keratinocytes and dermal fibroblasts (Bovine collagen matrix)	August 31, 2001 (PMA)	Ortec International, Inc., New York City, NY, US	FDA/ CDRH	Treatment of fresh, clean split thickness donor site wounds in burn patients.	Medical device

Table 1 Continued

Generic name (Trade name)	Cell origin (Material)	Approval date	Marketing authorization holder	Authority	Indication	Category
Interactive wound dressing (Dermagraft®)	Allogeneic fibroblasts (Extracellular matrix and bioabsorbable polyglactin mesh scaffold)	September 28, 2001 (PMA)	Advanced BioHealing, La Jolla, CA, US (2001-2002) Smith & Nephew, La Jolla, CA, US (2002-2006) Advanced BioHealing[1)], La Jolla, CA, US (2006-)	FDA/ CDRH	Use for treatment of full-thickness diabetic foot ulcers greater than six weeks duration which extend through the dermis, but without tendon, muscle, joint capsule or bone exposure	Medical device
Hematopoietic progenitor cells, cord blood (Hemacord)	Allogeneic cord blood (10% DMSO and 1% Dextran 40 in 25 mL total volume)	November 10, 2011 (BLA)	New York Blood Center, Inc., New York, NY, US	FDA/ CBER	Use in unrelated donor hematopoietic progenitor cell transplantation procedures with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorder affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.	Biologics
Allogeneic cultured keratinocyte and fibroblast in bovine collagen (Gintuit)	Allogeneic fibroblasts and keratinocytes (Bovine-derived collagen biomaterial)	March 9, 2012 (BLA)	Organogenesis Inc., Canton, MA, US	FDA/ CBER	Topical (non-submerged) application to surgically created vascular wound bed in the treatment of mucogingival conditions in adults	Biologics

PMA, Premarket Approval Application; CA, California; US, the United States; FDA, Food and Drug Administration; CDRH, Center for Devices and Radiological Health ; MA, Massachusetts ; HDE, Humanitarian Device Exemption; NY, New York; DMSO, Dimethyl Sulfoxide; BLA, Biologics License Applications; CBER, Center for Biologics Evaluation and Research.

1) Advanced BioHealing was acquired by Shire pharmaceuticals in 2011.

Table 2 History of regulatory action, preapproval and post-approval clinical evaluation of allogeneic human cell and tissue products in the US

Generic name (Trade name)	History of regulatory action	Pre-approval clinical evaluation	Post-approval clinical evaluation
Interactive wound and burn dressing (Formerly, Dermagraft-TC™, currently, TransCyte®)	• Not commercialized in the US or in other countries as of the submission. • Granted expedited review status on June 1, 1995 • Filed as PMA in March 16, 1996. • *Approved on March 18, 1997.* • *Approved of PMA supplement of additional indication on August 14, 1998*	Pre-clinical studies • Infectious agent testing • Biocompatibility studies • Functional testing • Stability, shipping and thawing studies • Comparability testing Clinical studies • Pilot study (10 patients) • Pivotal study: single piece study (66 patients) • Pivotal study: multiple piece study (11 patients) • Emergency use (2 patients) • A total of 89 patients	Pre-clinical studies • Not conducted Clinical studies • Multi-center, nonrandomized, unmasked study to receive at least 100 patients at 5-10 investigation sites. (Actually, a prospective, randomized, comparison study of silver sulfadiazine and TransCyte® was performed with the use of paired wound sites on 14 patients)
Living Skin Equivalent (LSE) Graftskin (Apligraf™)	• Authorized expedited on May 30, 1995 • Filed as PMA on October 4,1995 • Approved in Canada on 12 August, 1997 • *Approved on May 22, 1998* • *Approved of PMA supplement of additional indication on June 20, 2000*	Pre-clinical studies • Development & characterization studies • Immunology studies • Microbial studies • Toxicology studies Clinical studies • Randomized clinical trial of 240 patients to compare Apligraf and compression therapy (130 patients for Apligraf and 110 patients for control)	Pre-clinical studies • Purity of the transferrin (viral inactivation) • Karyology of keratinocytes and fibroblast Clinical studies • Longevity of Apligraf on patients

Table 2 Continued

Generic name (Trade name)	History of Regulatory action	Preapproval Clinical Evaluation	Post-approval Clinical Evaluation
Interactive wound and burn dressing (Composite Cultured Skin)	• Not commercialized in the US as of the submission. • Designated as Humanitarian Use Device (HUD) on December 24, 1998 • *Approved as HDE on February 21, 2001.*	Pre-clinical studies • Biocompatibility studies • Shelf life • Sterility testing Clinical studies • Clinical study in the treatment of Epidermolysis Bullosa (EB): 12 patients • Clinical studies for treatment of other conditions: 74 patients • Immune response: 186 patients	Pre-clinical studies • Unknown. Clinical studies • Unknown
Interactive wound and burn dressing (Orcel™)	• Not marketed in the US and any country as of the submission • Filed as PMA on March 5, 2001 • *Approved on August 31, 2001*	Pre-clinical studies • Same data as Composite Cultured Skin • *In vitro* assay and biocompatibility studies of acellular collagen • A full thickness skin wound studies Clinical studies • Pilot study (8 patients) • Pivotal study (82 patients)	Pre-clinical studies • Methods against bovine serum proteins, human blood group antigens and HLA antigens Clinical studies • Evaluating the duration of Ortec cells on the donor site wounds
Interactive wound dressing (Dermagraft®)	• Available in the US as investigational device under IDE G900155 • Approved in Canada in August 1997 • Filed as PMA on August 25, 2000 • *Approved on September 28, 2001*	Pre-clinical studies • Development & characterization studies • Toxicology studies • Stability/shipping studies Clinical studies • Feasibility study (50 patients) • Pivotal study I (281 patients) & II (314 patients) • Supplementary Study (50 patients) • Treatment IDE (49 patients)	Pre-clinical studies • Unknown Clinical studies • Unknown

Table 2 Continued

Generic name (Trade name)	History of Regulatory action	Preapproval Clinical Evaluation	Post-approval Clinical Evaluation
Hematopoietic progenitor cells, cord blood (HPC-C) (Hemacord)	• Announced "Guidance for Industry: Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indication" in the Federal Register Vol 74, No. 201, October 20, 2009, 53753-4 • Submitted BLA on January 10, 2011 • *Approved as Biologic Products on November 10, 2011*	Pre-clinical studies • No pharmacology/toxicology studies Clinical studies • Docket FDA-1997-N-0497 (Formerly Docket No. 97N-0497) • Docket FDA-2006-D-0157 (Formerly Docket No. 06D-0514) (1299 patients) • COBLT study (324 patients) • Hemacord (155 patients)	Pre-clinical studies • Unknown Clinical studies • Unknown
Allogeneic cultured keratinocyte and fibroblast in bovine collagen (Gintuit)	• Submitted IDE (G070012.0) for cutaneous wounds on January 17, 2007 • Submitted PMA to CDRH on December 19, 2009 and the FDA issued a letter of refuse to file because of assigned jurisdiction to CBER • Submitted BLA on May 13, 2011 • *Approved as Biologic Products on March 9, 2012*	Pre-clinical studies • Same data as Apligraf PMA • Pharmacology study (*in vitro* & *in vivo*) • Biocompatibility testing in conformance to ISO 10993 standards Clinical studies • Pivotal studies I (25 patients) & II (96 patients)	Pre-clinical studies • Unknown. Clinical studies • Unknown

US, the United States, PMA, Premarket Approval Application; HUD, Humanitarian Use Device, HDE, Humanitarian Device Exemption; EB, Epidermolysis Bullosa; IDE, Investigational Device Exemption; BLA, Biologics License Applications; CDRH, Center of Device and Radiological Health; CBER, Center of Biologics Evaluation and Research; ISO, İnternational Organization for Standardization

Table 3 Medical Device Safety: Recalls[a)]

Generic name (Trade name; recalling firm)	Recall Class[b)]	Date posted (Date recalled)	Reason	Quantity
Interactive wound and burn dressing (Formerly, Dermagraft-TC™, currently, TransCyte®)	NA			
Living Skin Equivalent (LSE) Graftskin (Apligraf™; Organogenesis, Inc.)[c)]	Class 3	October 24, 2006 (September 29, 2006)	Product pH out of specification	58
	Class 2	January 24, 2008 (December 27, 2007)	Contamination: Apligraf™ units were reported to have a gram negative rod (bacillus) in the agarose nutrient medium retained at Organogenesis.	177
	Class 2	November 12, 2009 (September 28, 2009)	Unit contaminated with *Staphylococcus epidermis*	60
	Class 2	September 28, 2010 (August 2, 2010)	Product is contaminated with a yeast identified as *Pseudozyma antarctica*.	32
	Class 2	March 23, 2011 (January 30, 2011)	Product sterility compromised	50
	Class 2	March 23, 2011 (February 24, 2011)	Products sterility may be compromised	7
Interactive wound and burn dressing (Composite Cultured Skin)	NA			
Interactive wound and burn dressing (Orcel™)	NA			
Interactive wound dressing (Dermagraft®; Smith and Nephew Wound Management)	Class 2	June 4, 2003 (May 2,2003)	Did not meet finished device specifications for DNA criteria	22
Hematopoietic progenitor cells, cord blood (Hemacod)	NA			
Allogeneic cultured keratinocyte and fibroblast in bovine collagen (Gintuit)	NA			

NA: not applicable

a) A recall is an action taken to address a problem with a medical device that violates FDA law. Recalls occur when a medical device is defective, when it could be a risk to health, or when it is both defective and a risk to health.

b) Class 1 recall: a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death; Class 2 recall: a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health

consequences or where the probability of serious adverse health consequences is remote; Class 3 recall: a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.
c) According to CMC review of Gintuit, eight more recalls were reported due to mainly microbial contamination of agarose in 1999 to 2011.

Alerts and Notices (Devices): http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/default.htm
Tips and Articles on Device Safety: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/TipsandArticlesonDeviceSafety/default.htm

Table 4 Change Records of Premarket Application Approval

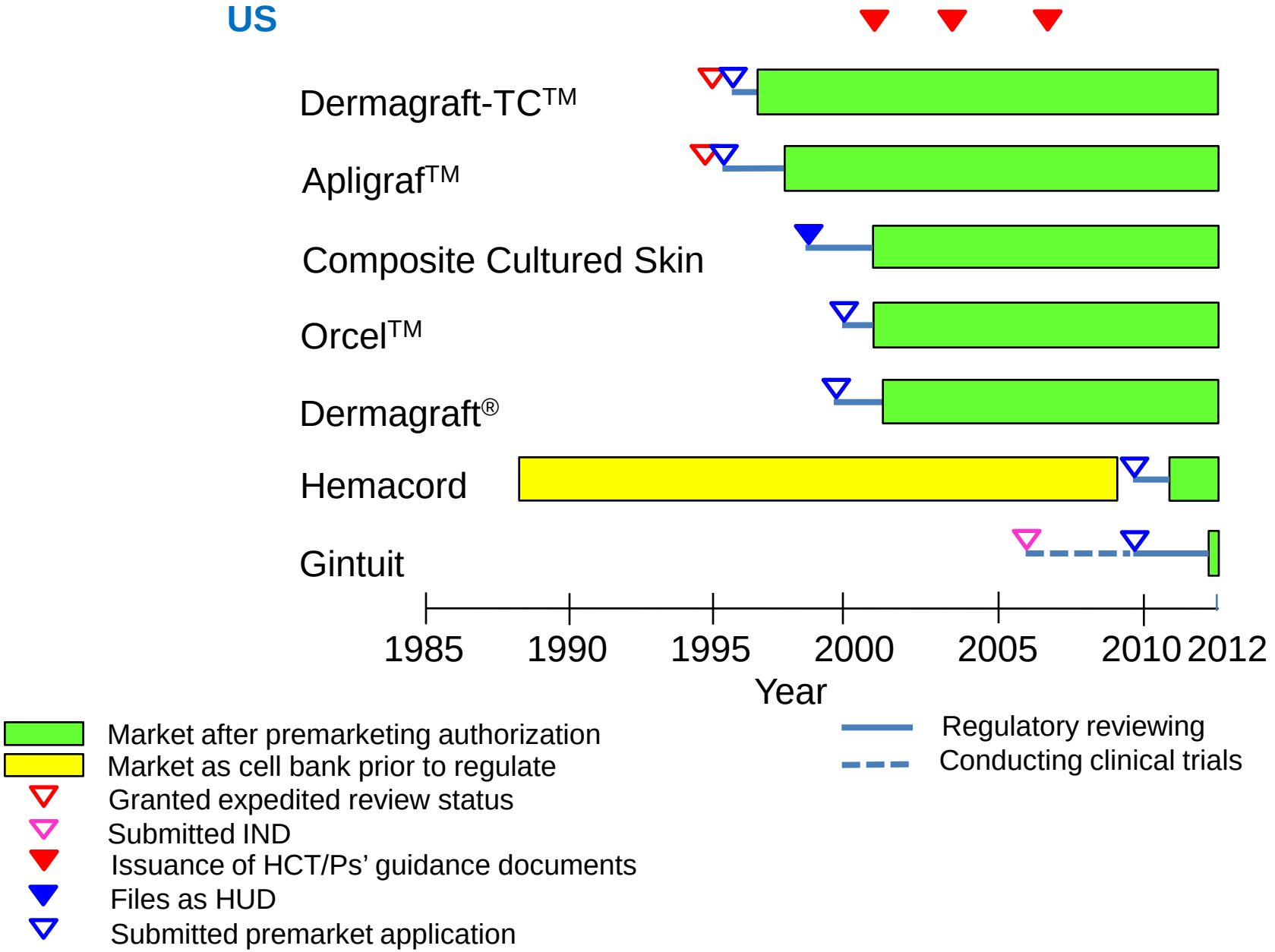
Generic name (Trade name)	PMA supplement type[a)]					Reason				
	180-day	Real-time	Special supplement	30-day/ 135-day	ND[b)]	Labelling	Manufacture Process Changing	Post-approval study	ND	Total
Interactive wound and burn dressing(Formerly, Dermagraft-TC™, currently, TransCyte®)	12	4	1	2	2	4	10	5	2	21
Living Skin Equivalent (LSE) Graftskin (Apligraf™)	9	27	2	20	10	7	50 (New cell lines: 21, Fibroblast:4; Keratinocyte:17)	1	10	68
Interactive wound and burn dressing (Composite Cultured Skin)	-	-	-	-	-	-	-	-	-	-
Interactive wound and burn dressing (Orcel™)	-	2	-	-	-	-	2 (New cell lines: 2)	-	-	2
Interactive wound dressing (Dermagraft®)	1	0	2	5	4	1	7	-	4	12
Hematopoietic progenitor cells, cord blood (HPC-C) (Hemacord)	-	-	-	-	-	-	-	-	-	-
Allogeneic cultured keratinocyte and fibroblast in bovine collagen (Gintuit)	-	-	-	-	-	-	-	-	-	-

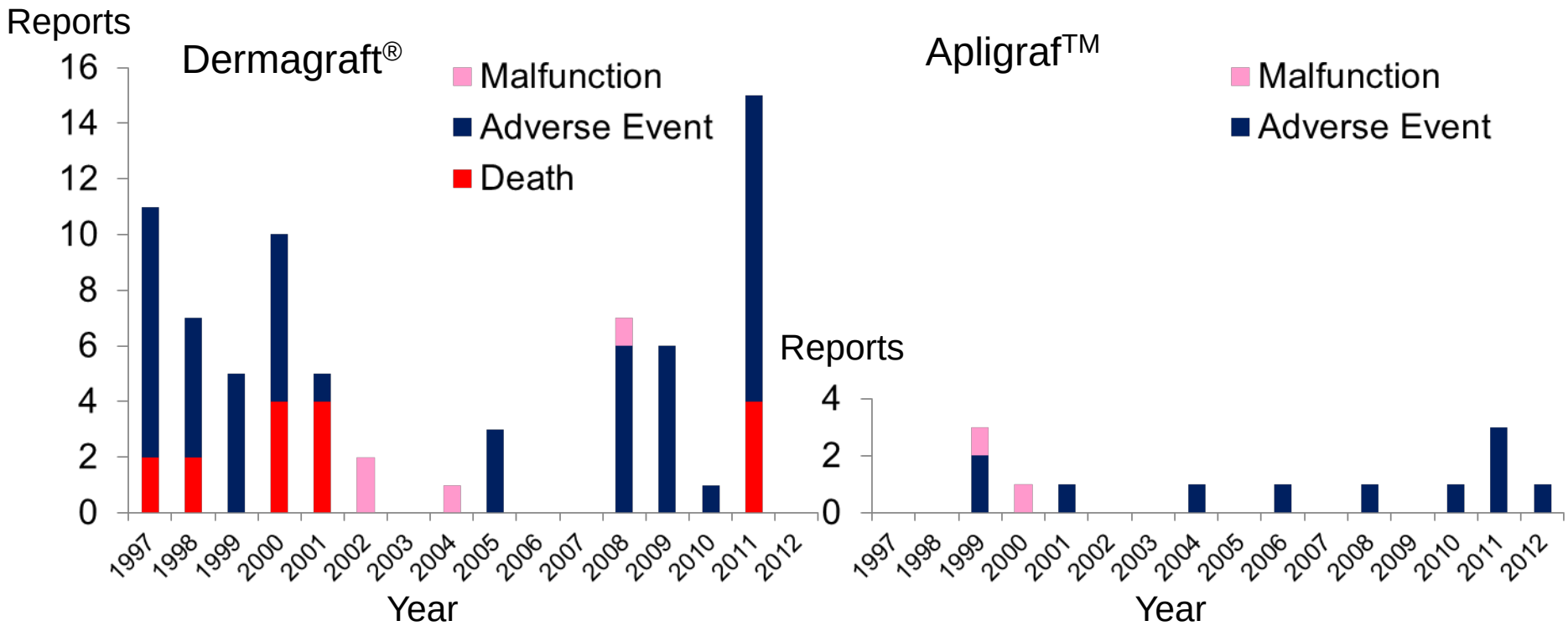
PMA, Premarket application; ND, Not determined

a) PMA supplement consists of four types of its supplement: i) Normal PMA supplement (180-day) meets for significant change that affects the safety and effective of medical device, ii) Real-time review is appropriate for a minor change that is expected with a product line and the supplement is reviewing during meeting or conference call with applicant. iii) Special PMA supplement is also appropriate for any change that enhances the safety of the medical device or in the use of the medical device, mainly due to labeling changes. iv) 30-day notice and 135 PMA supplement is appropriate for modification to manufacturing procedures or method of manufacture that affect the safety and effectiveness of the medical device. If the 30-day notice is not adequate, the supplement will become 135-day PMA supplement.

b) Any information was not posted on the website.

US


Dermagraft-TC™
Apligraf™
Composite Cultured Skin
Orcel™
Dermagraft®
Hemacord
Gintuit
1985
1990
1995
2000
2005
2010
2012
Year
Market after premarketing authorization
Market as cell bank prior to regulate
Granted expedited review status
Submitted IND
Issuance of HCT/Ps' guidance documents
Files as HUD
Submitted premarket application
Regulatory reviewing
Conducting clinical trials


Reports
Dermagraft®
Malfunction
Adverse Event
Death
16
14
12
10
8
6
4
2
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Year
Apligraf™
Malfunction
Adverse Event
Reports
4
2
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Year