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The regulation of allogeneic human cells and tissue products as biomaterials

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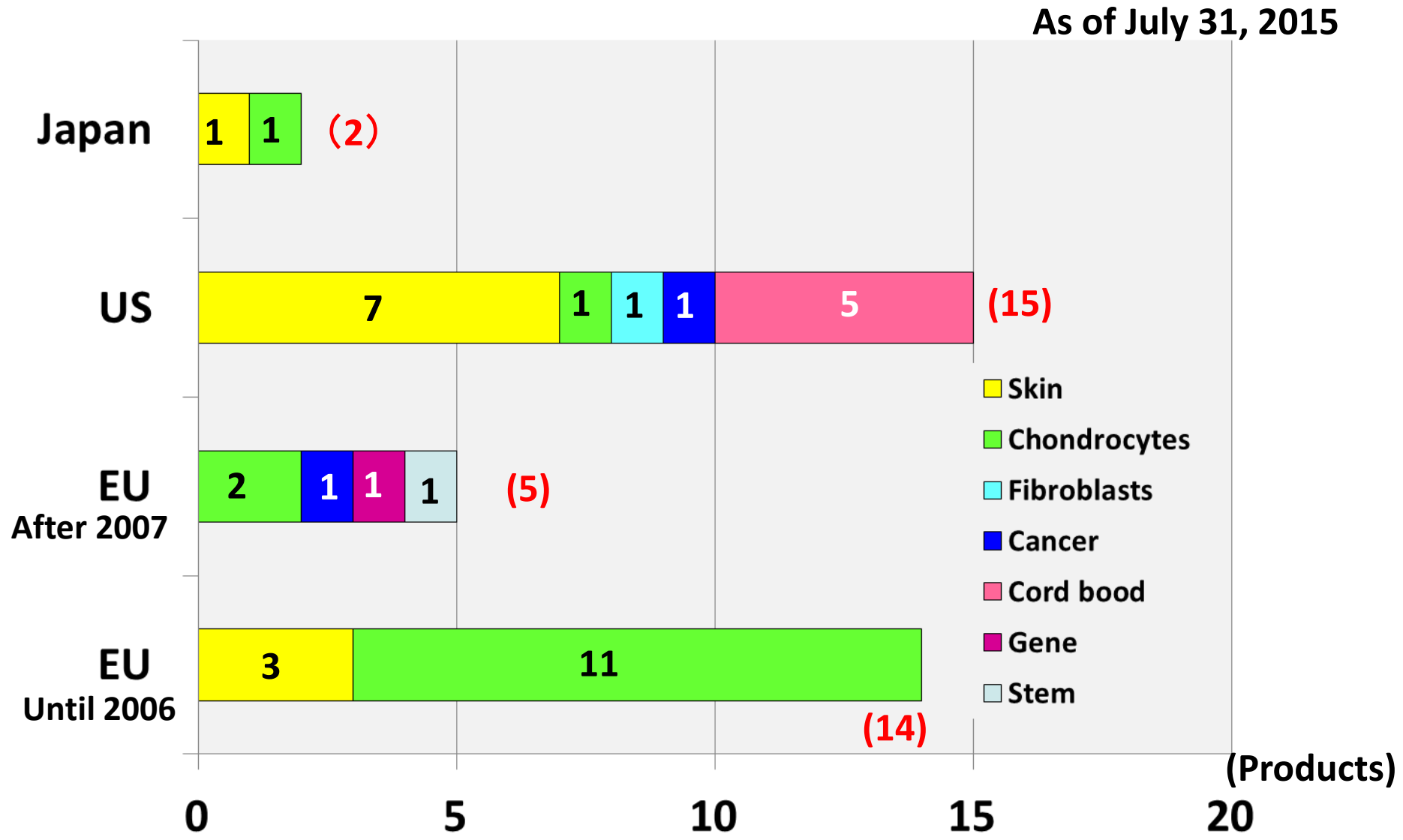
Definition of Biomaterials

- **Materials intended to interference with biological systems** to evaluate, treat, augment or replace any tissue, organ or function of the body (The Williams dictionary of biomaterials, 1999)
- **Substances that have been engineered to take a form which, alone or part a complex system, are 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 (On the nature of biomaterials, Biomaterials: 2009)

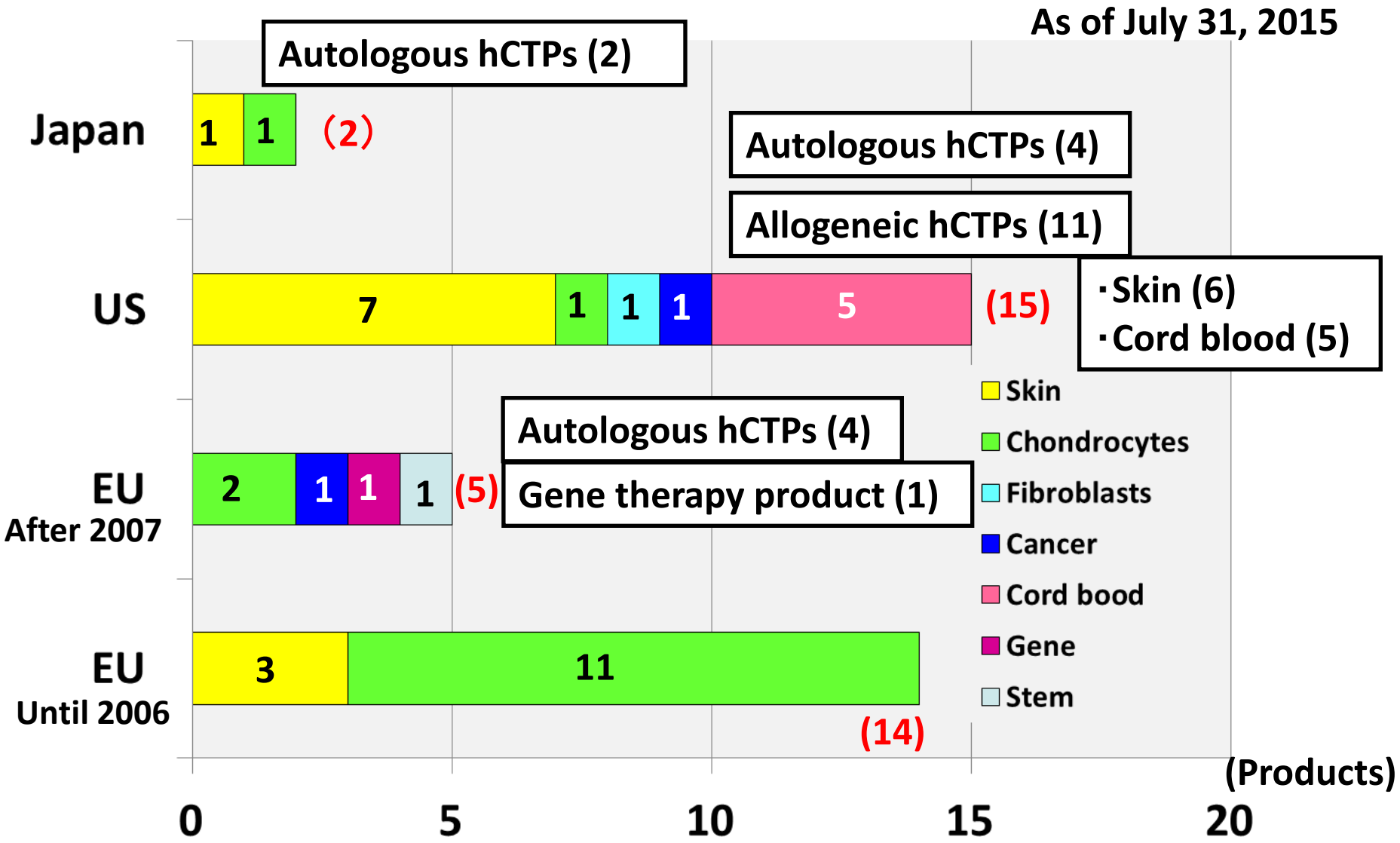
➢ **Engineered tissues, cells, organs** and even viruses

Approved human cell and tissue products (hCTPs)



EU: Regulation(EC) No1394/2007 regarding advanced therapy medicinal products was issued in 2007

Approved human cell and tissue products (hCTPs)



EU: Regulation(EC) No1394/2007 regarding advanced therapy medicinal products was issued in 2007

Outline

- **Regulation of human cell and tissue products (hCTPs) in Japan, the United States (US), and the European Union (EU)**
- **Premarket approval of hCTPs in the US**
  - Autologous hCTPs
  - Allogeneic hCTPs
    - ✓Somatic cell therapy products
    - ✓Unrelated allogeneic placental/umbilical cord blood products
  - Gene therapy medicinal products
- **Summary and conclusions**

Allogeneic hCTPs have a great possibility to develop therapeutics for life threating diseases or orphan diseases

Regulation of hCTPs in Japan, the US, and EU

Nation /area	Classification	Regulation
Japan	**Regenerative medical products** •Cell/tissue-engineered products •Gene therapy products	•**Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act: November 2013)**
US	**Human cells, tissues and cellular tissue-based products (HCT/Ps)** •351HCT/Ps •361HCT/Ps	•**Public Health Service Act, Section 351 and 361** •**21CFR1271：Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)** ✓21CFR1271.10：361HCT/Ps ✓21CFR1271.15：Exception ✓**21CFR1271.20：351HCT/Ps (regulated as drugs, medical devices, or biological products)**
EU	**Advanced therapy medicinal products (ATMPs)** •Somatic cell therapy medicinal products •Tissue engineered products •Gene therapy medicinal products	▪**Regulation (EC) No 1394/2007:** Advanced-therapy medicinal products ▪Regulation (EC) No 726/2004：EU central market authorisation

Allogeneic hCTPs: Somatic cell therapy products

TransCyte®

1997

Apligraf™

1998

Composite Cultured Skin

2001

Orcel™

2001

Medical devices: 5 products

Biologics: 1 product

Dermagraft®

2001

Gintuit

2012

Allogeneic hCTPs: Somatic cell therapy products

TransCyte®

Full-thickness and deep partial-thickness thermal burns wounds

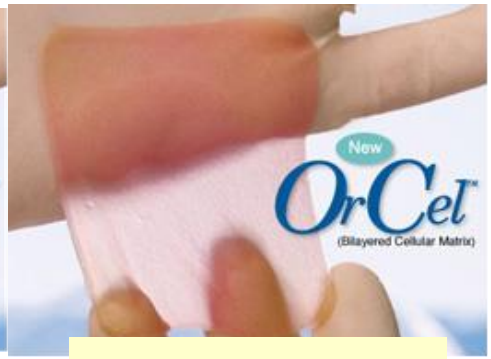
Apligraf™

Non-infected partial and full-thickness skin ulcers, and diabetic foot ulcers

Composite Cultured Skin

Mitten hand deformity due to recessive dystrophic epidermolysis bullosa (RDEB)

Orcel™



Burns wound

Dermagraft®

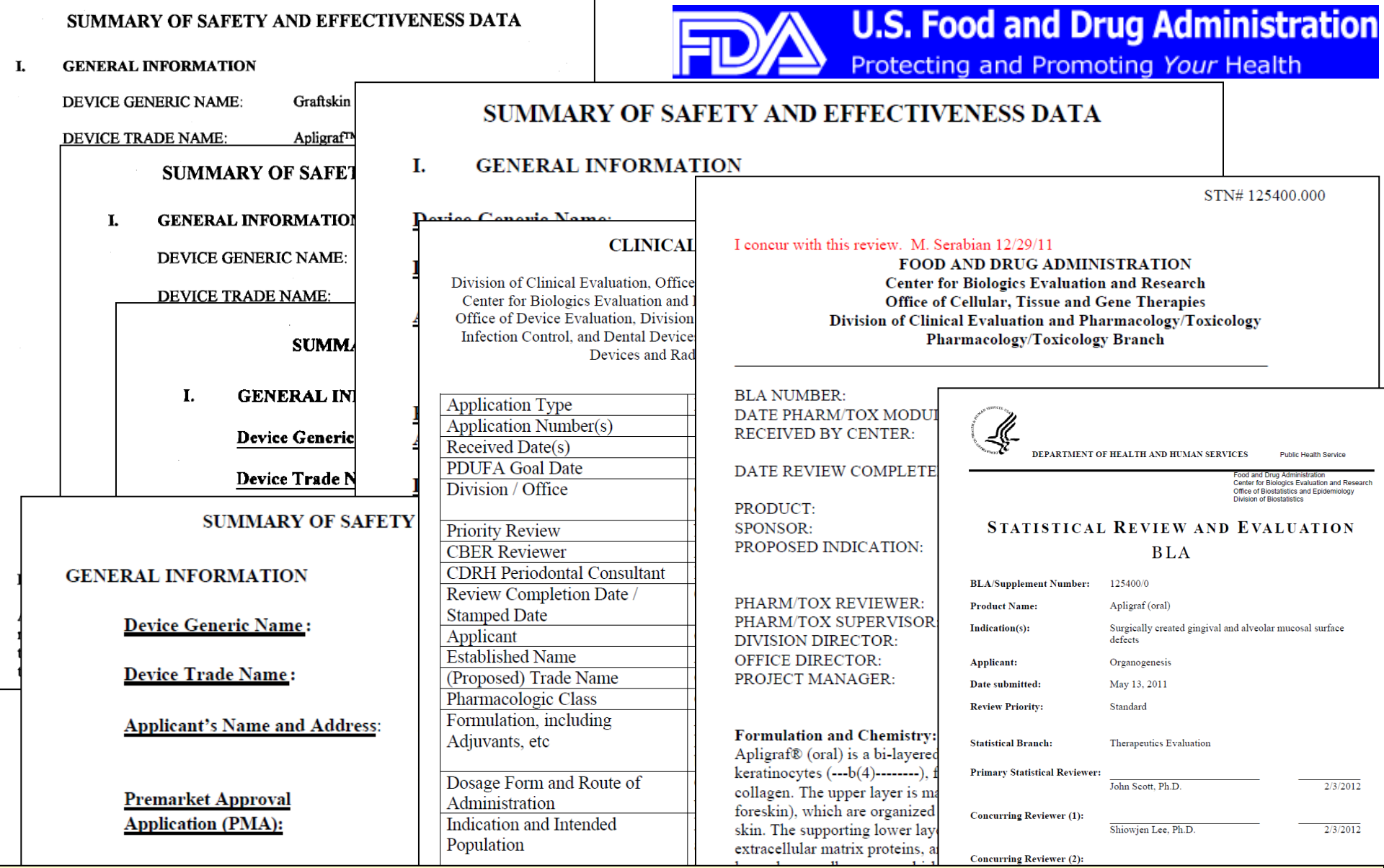
Full-thickness diabetic foot ulcers

Gintuit

Surgically created vascular wound bed in the mucogingival condition

Medical devices: 5 products

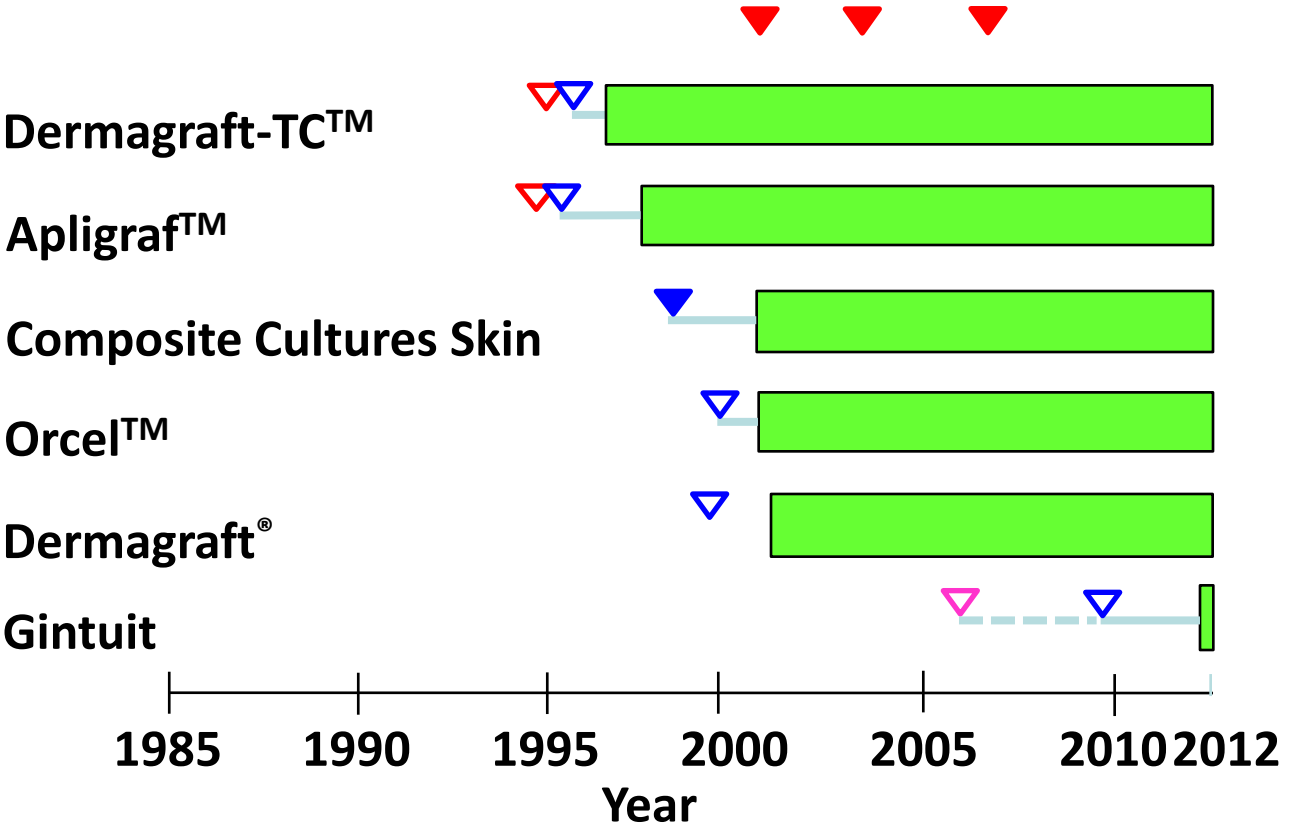
Biologics: 1 product



Reviewed the summary of safety and effective data of medical devices as allogeneic hCTPs

- Conducted and approved as medical devices

US



Market after premarketing authorization

Granted expedited review status

Submitted IND

Issuance of HCT/Ps' guidance documents

Files as HUD

Submitted premarket application

Regulatory reviewing

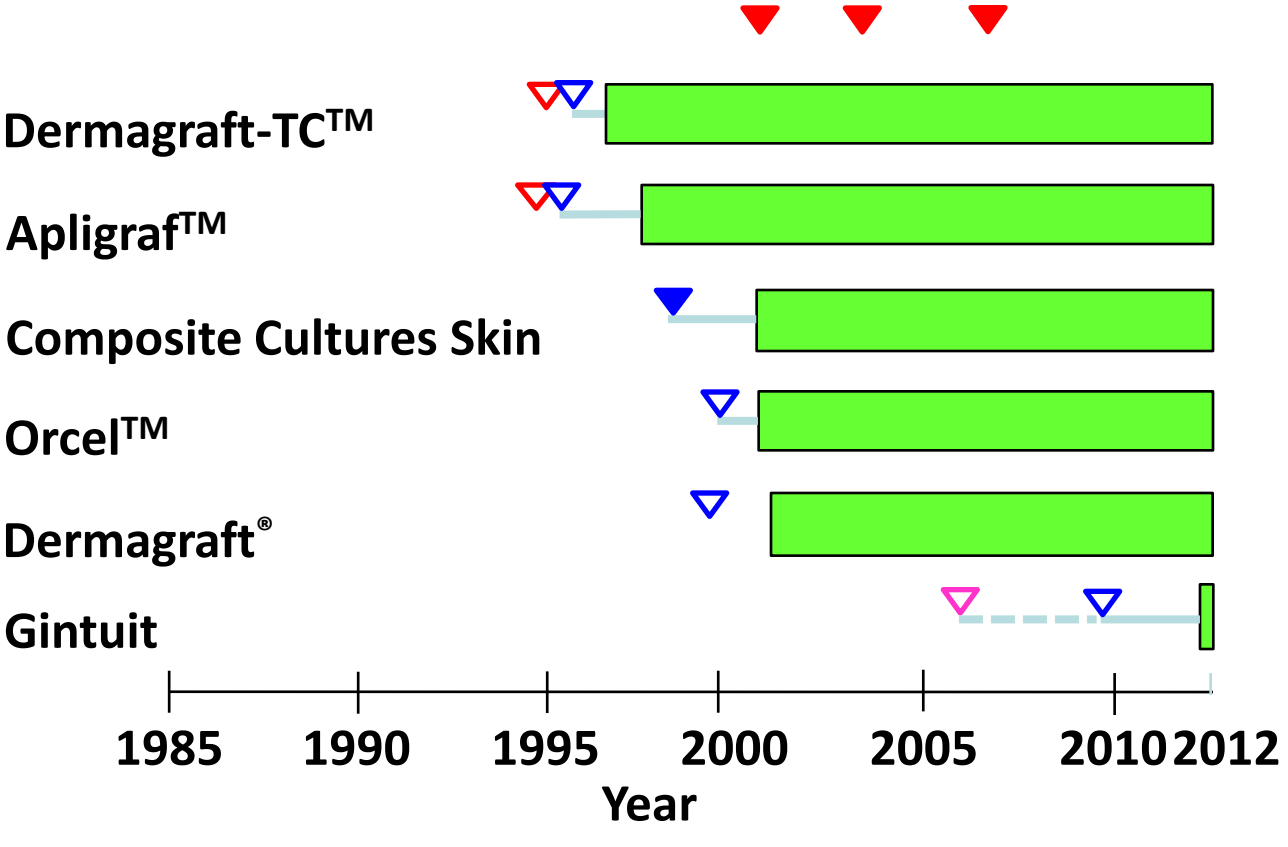
Conducting clinical trials

- Conducted and approved as medical devices

- Gintuit (changed indication of Apligraf™) to be changed from PMA to BLA after submission

- Gintuit to be approved as Biologics

US



- Jurisdiction of HCT/Ps was transferred to the Center for Biologics Evaluation and Research（CBER）on March 24, 2005

- Major guidance of HCT/Ps were in the effective on May 25, 2005

- 21 CFR 3.1 Definitions Definition of primary mode of action on combination products on August 25, 2005

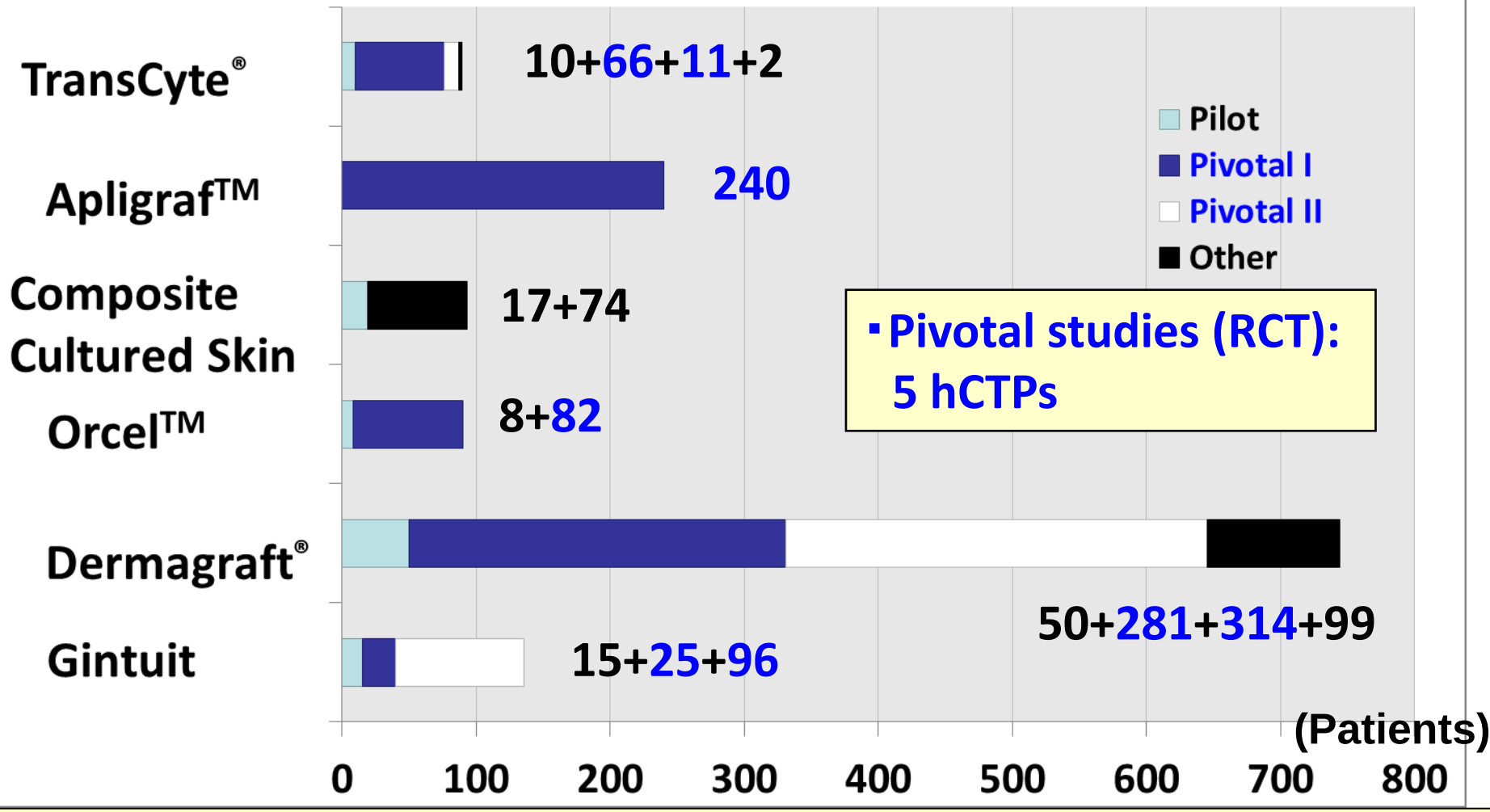
Safety and efficacy evaluation of allogeneic hCTPs

Trade name	Preapproval evaluation	Postapproval evaluation
TransCyte® (Dermagraft-TC™)	**Nonclinical studies** •Infectious agent testing •Biocompatibility studies •Functional studies •Stability, shipping, thawing studies •Comparability testing	**Nonclinical studies** •Not conducted
	Clinical studies •Pilot study (10 patients) •Pivotal study: single piece study (66 patients) •Pivotal study: multiple pieces study (11patients) •Emergency use (2 patients)	**Clinical studies** •Multi-center, nonrandomized, unmasked study to receive at least 100 patients at 5-10 sites (actually performed with 14 patients)

- Pilot study (10 patients); Pivotal study (66 patients and 11 patients)

- Of 6 hCTPs, 5 products were conducted as pivotal clinical trials with investigational device or comparator such as control treatment to confirm safety and efficacy

Clinical studies for allogeneic hCTPS

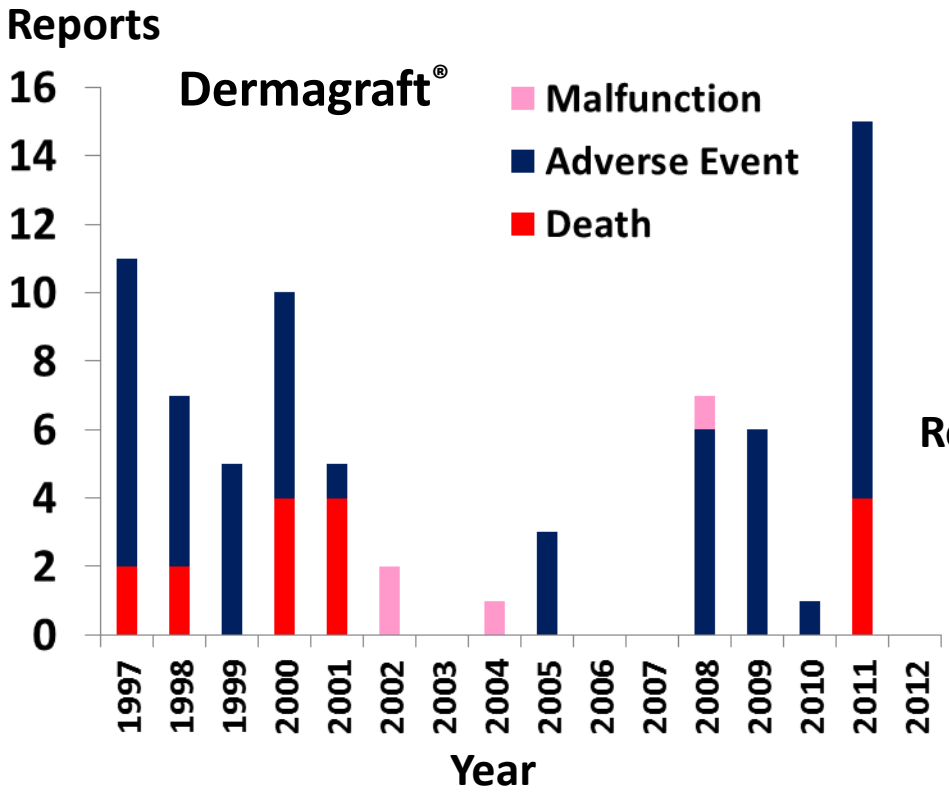


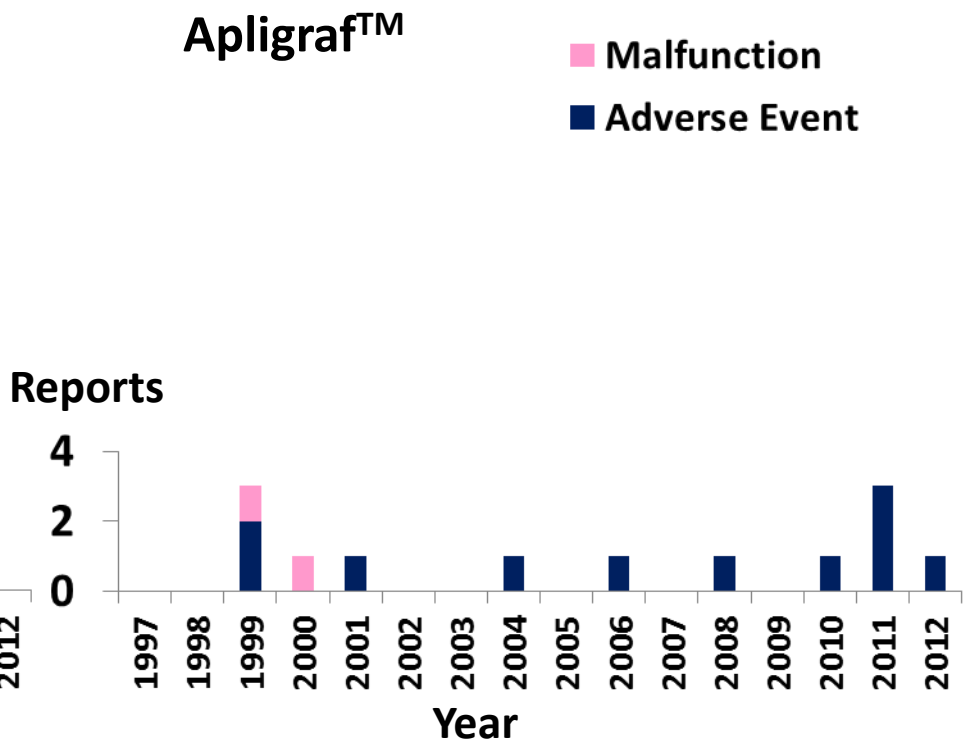
- Conducting RCTs (randomized controlled trials) enable allogeneic hCTPs to evaluate safe and efficacy during premarket approval review

Statistical Guidance for Clinical Trials of Non Diagnostic Medical Devices

Office of Surveillance and Biometrics,
Center for Devices and Radiological Health
U.S. Food and Drug Administration, January 1996

Adverse events reporting





- Dermagraft ®: 73 reports included Dermagraft-TC™ and TransCyte®
- Apligraf™: 13 reports included Graftskin

Medical device safety: Recalls

Trade name	Recall class and reasons
TransCyte®	Not applicable (NA)
Apligraf™	Class 3 : Product pH out of specification（2006/10/24） Class 2 : Contamination in agarose nutrient medium (2008/1/24) Class 2 : Unit contamination with *S. epidermis* (2009/11/12) Class 2 : Product contamination with a yeast (2010/9/28) Class 2 : Product sterility compromised (2011/3/23, twice)
Composite Cultured Skin	NA
Orcel™	NA
Dermagraft®	Class 2 : Did not meet finshed device specification (2003/6/4)
Gintuit	NA

Apligraf™: 6 and 8 times
Dermagraft®: 1 time

Change records of premarket application approval

Trade name	PMA supplement type					Total	Reason			
	180-day	Real-time	Special	30-day/ 135-day	ND		Label-ing	Manu-factur e proces s	Post-approval study	ND
TransCyte®	12	4	1	2	2	21	4	10	5	2
Apligraf™	9	27	2	20	10	68	7	50	1	10
Composite Cultured Skin	-	-	-	-	-	-	-	-	-	-
Orcel™	-	2	-	-	-	2	-	2	-	-
Dermagraft®	1	0	2	5	4	12	1	7	-	4
Gi										-

- For Apligraf™, 68 PMA supplements were submitted;
  50 manufacture process changes including 21 new cell lines
- For Dermagraft®, 21 PMA supplements were submitted;
  10 manufacture process changes

Summary of allogeneic HCTPs

- Of six allogeneic HCTPs, five were approved as medical devices, and the other one as biologics
- Jurisdiction of HCT/Ps was transferred to CBER from Center for Device and Radiological Health: CDRH)
  - Gintuit had to change premarket approval (PMA) application into biologics license application (BLA)
  - Five products were conducted RCTs as medical devices using statistical guidance
  - Adverse event reporting: Dermagraft®(73 reports), Apligraf™ (13 reports)
  - Recalls were voluntarily conducted on Apligraf™ (8 and 6 times) and Dermagraft® (1 time)
  - PMA holders were submitted PMA supplement 68 times for Apligraf™ and 21 times for Dermagraft®: the most of reasons are manufacturing changing including cell line change

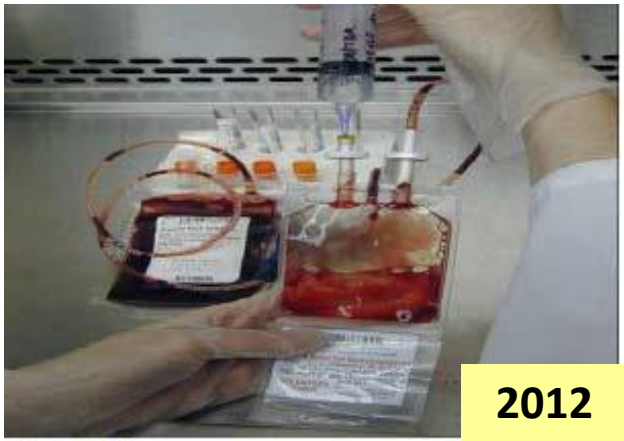
Conclusions of allogeneic HCTPs

- Since allogeneic cell sources would enable to produce large-scale lots of products having well-controlled quality with lots of products, they can be established as a good business model that brings profits
- In the future, it is widely expected that various kinds of allogeneic human cells and tissue products would be on market

Allogeneic hCTPs : Unrelated allogeneic placental/umbilical cord blood products

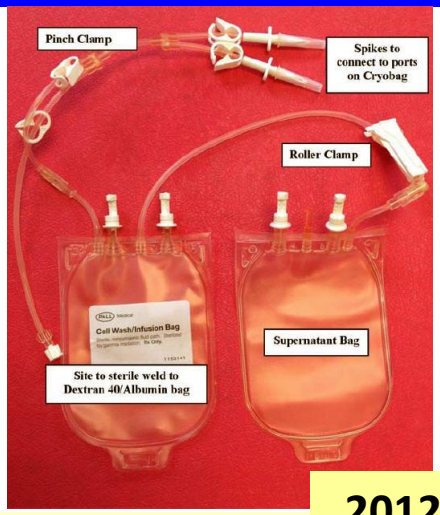
2011

HEMACORD®
New York Blood Center, Inc



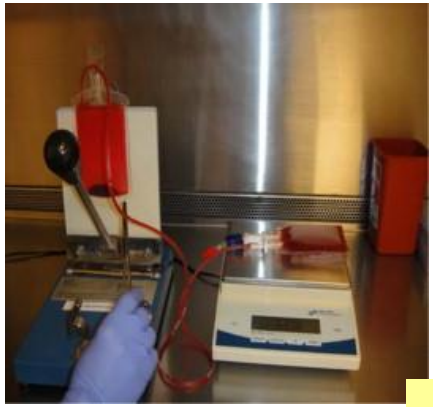
2012

HPC, Cord Blood
Clinimmune Labs,
University of Colorado
Cord Blood Bank



2012

Ducord
Duke University
School of Medicine



2013

Allocord
SSM Cardinal Glennon
Children's Medical Center,
St. Louis University

2013

HPC, Cord Blood BLA
125432
LifeSouth Community
Blood Centers, Inc.,
Florida University

Indication for allogeneic cord blood hematopoietic progenitor cell therapy

- **Allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment**
- **The risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and other available treatment or types of hematopoietic progenitor cells**

All unrelated allogeneic placental/umbilical cord blood products have same indication as above mentioned

Regulation on allogeneic cord blood hematopoietic progenitor cell therapy in the US

- Minimally manipulated, unrelated allogeneic placental/umbilical cord blood indented hematopoietic reconstitution for specified indication (2009): Recommendation for the submission of a BLA for umbilical cord blood
- In October 2009 Federal Register notice, the FDA announced that manufacturers of cord blood will be required to have an approved BLA or IND in effective for unrelated cord blood shipped after October 20, 2011

- ✓Hemacord：approved on November 10, 2011
- ✓HPC, Cord Blood： approved on May 24, 2012
- ✓Ducord： approved on October 4, 2012
- ✓Allocord： approved May 30, 2013
- ✓HPC, Cord Blood BLA125432： approved June 13, 2013

Efficacy evaluation

	Study design	Patients	Recovery of neutrophils at Day 42 (>500/uL)	Median day of neutrophil recovery	Recovery of platelets at Day 100 (>20000/uL)	Median day of platelets recovery
COBLT	One arm, prospective	324	76%	27	57%	90
Dockets	Retrospective	1299	77%	25	Not available	Not available
Hemacord	Retrospective	2460 (155)	74% (83%)	25 (20)	62% (77%)	65 (45)
HPC, Cord Blood	Retrospective	293	77.6%	24.5	61%	55
Ducord	Retrospective	550	95%	21	92%	46
Allocord	Retrospective	1086	88%	Not available	87%	Not available
HPC, Cord Blood BLA125432	Retrospective	22	91%	22	95%	44

Recovery of neutrophils and platelets of each product were similar to the datasets of COBLT(Cord Blood Transplantation Study), Dockets FDA-1997-N-0010, and FDA-2006-D-0157

Safety evaluation

	Study design	Patients	Total mortality	Early mortality (Day 100)	Acute GVHD
COBLT	One arm, prospective	324	Not available	Not available	Not available
Dockets	Retrospective	1299	635/1229 (48.9%)	328/1299 (25.3%)	813/1182 (69%)
Hemacord	Retrospective	2460 (155)	1499/2691 (56%)	932/2691 (35%)	1286/2326 (55%)
HPC, Cord Blood	Retrospective	293	162/313 (52%)	93/257 (36.3%)	29/63 (46%)
Ducord	Retrospective	937	513/937 (55%)	343/646 (22%)	386/646 (60%)
Allocord	Retrospective	501	214/501 (43%)	85/499 (17%)	257/501 (51%)
HPC, Cord Blood BLA125432	Retrospective	22	12/22 (55%)	7/22 (32%)	25/53 (46%)

Total mortality, early mortality, and rate of acute GVHD(graft versus host disease) of were similar to the datasets of COBLT(Cord Blood Transplantation Study), Dockets FDA-1997-N-0010, and FDA-2006-D-0157

Review report of unrelated allogeneic placental/umbilical cord blood products

- **Many review comments on CMC (chemistry, manufacturing, and controls) described:**
  - ✓ Should be compliant with CGMP
  - ✓ Need to establish validation for manufacturing procedures and quality control
- **Sources of data for clinical review included published literatures, the dockets (Dockets FDA-1997-N-0010 and FDA-2006-D-0157), and the COBLT study (Cord Blood Transplantation Study)**
- **None of RCT (Randomized Controlled Trial) compliant with GCP was conducted**
- **No preclinical study data was submitted**

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On

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