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OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

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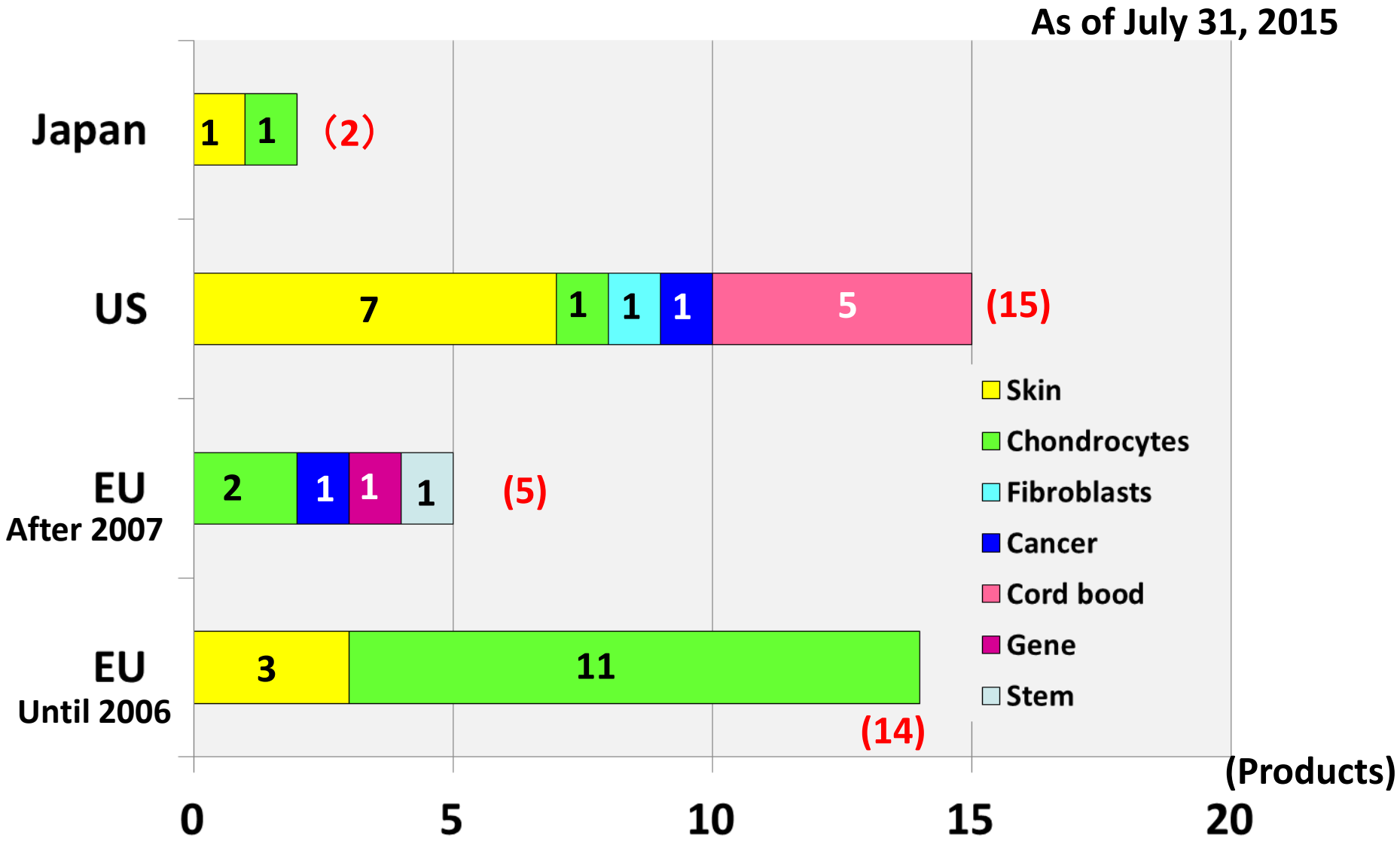
European Pharma Congress-2015

Regulatory approval for autologous human cells and tissue products in the United States, the European Union, and Japan

Kazuo Yano and Masayuki Yamato

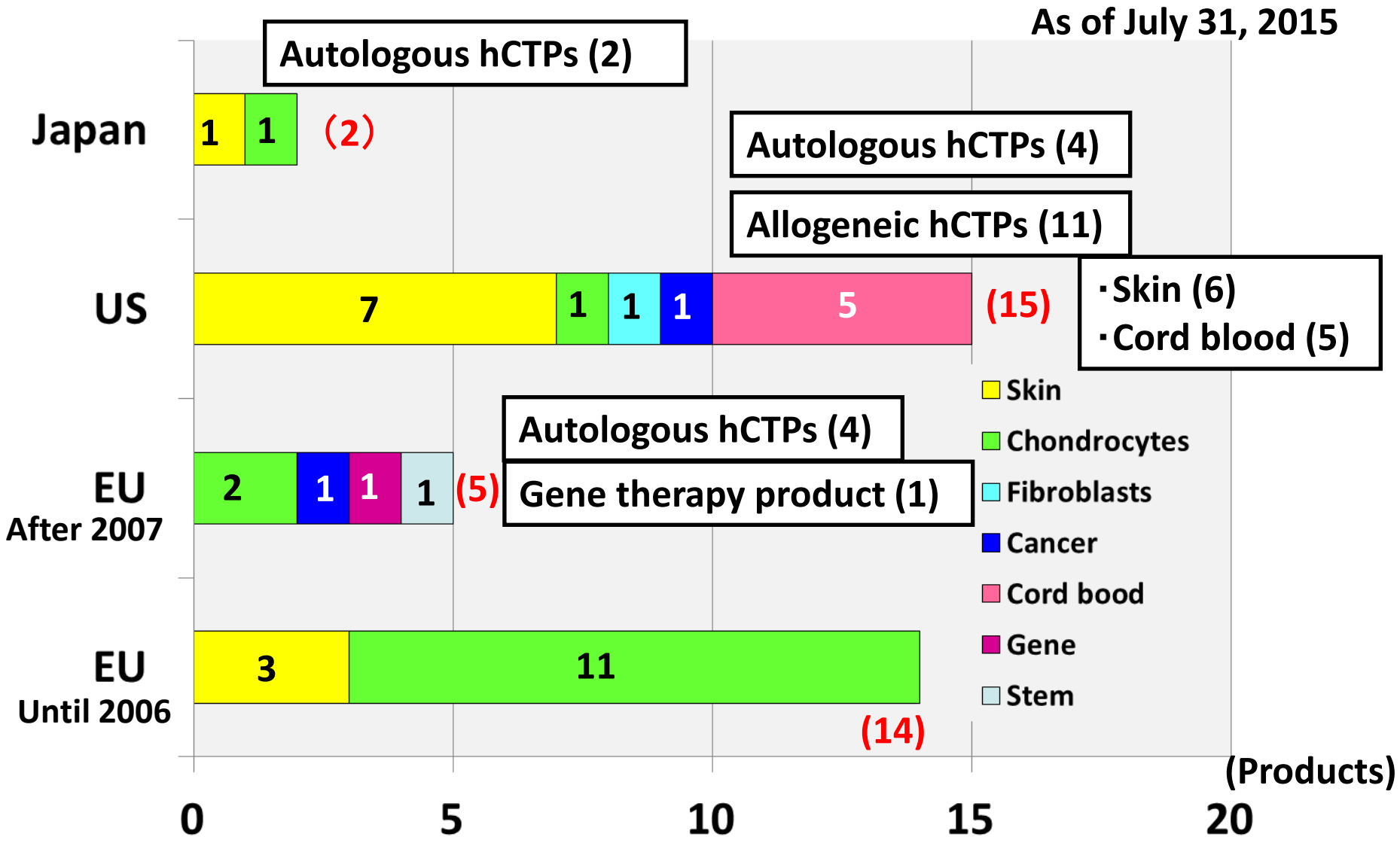
Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Japan.

Approved human cells and tissue products (hCTPs)



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

Approved human cells and tissue products (hCTPs)



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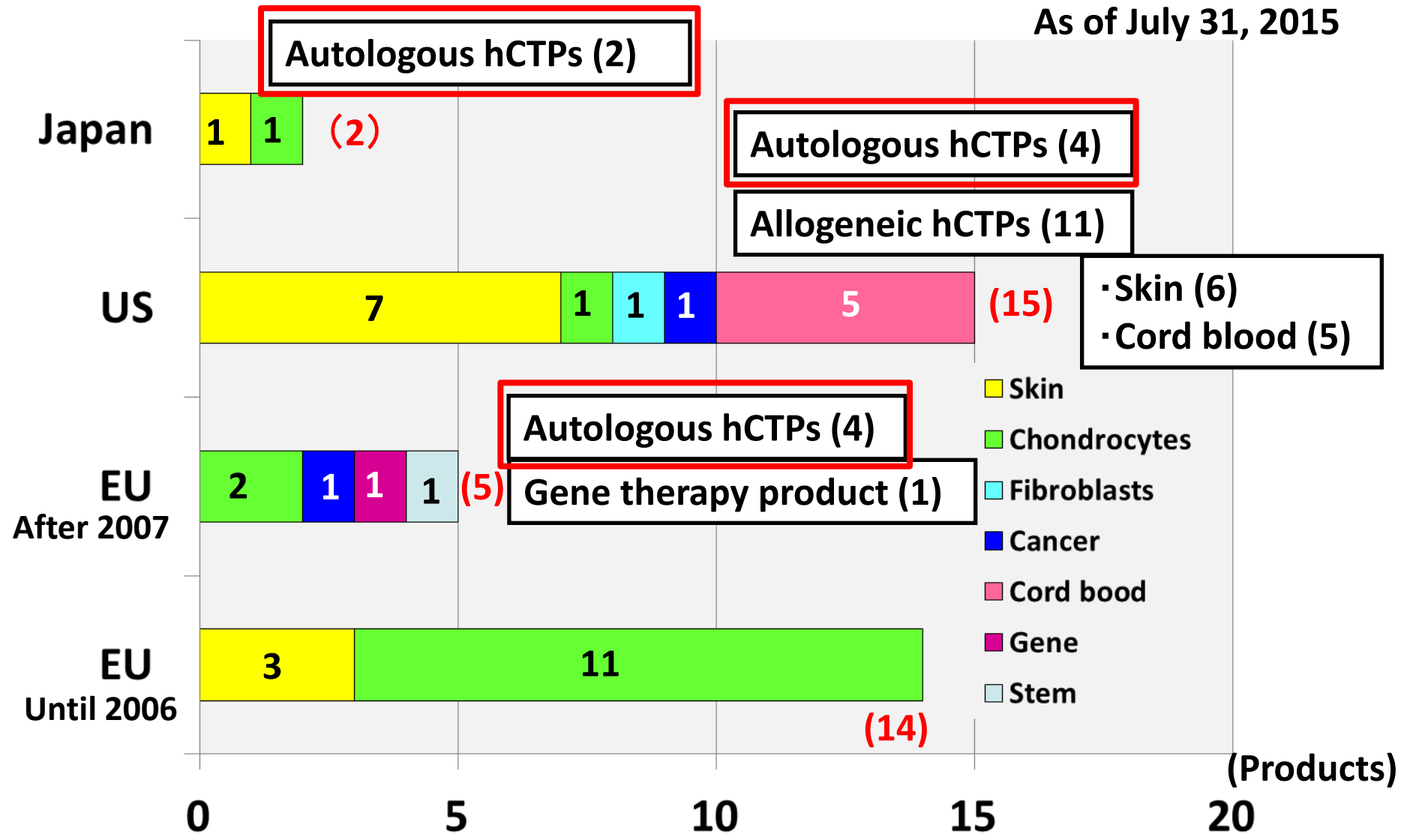


EU: Regulation(EC) No1394/2007 regarding advanced therapy medicinal products was issued in 2007

Hypothesis and Aim

- **Hypothesis**
  - **Autologous hCTPs may be limited information for premarket approval evaluation**
  - **They may need a special market evaluation system**
- **Aim**
  - **Provide information to enhance the discussion regarding the regulatory approval of hCTPs which have little consideration about transplant graft rejection, and microbiological and viral infections**

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 Japan, the US, and the EU**
  - **Autologous hCTPs**
  - Allogeneic hCTPs
    - ✓Somatic cell therapy products
    - ✓Unrelated allogeneic placental/umbilical cord blood products
  - Gene therapy medicinal products
- **Summary and conclusions**

Regulation of hCTPs in Japan, the US, and EU

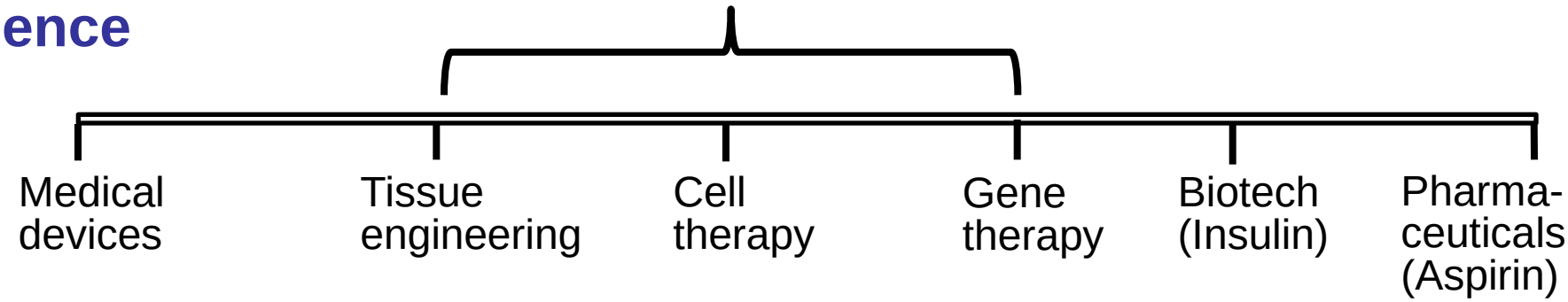
Nation /area	Classification	Regulation
Japan	**Regenerative medicinal products** **•Cell/tissue-engineered products** **•Gene therapy products**	**•Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act: November 2013)**
US	**Human cells, tissues and cellular tissue-based products (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 drug, 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

Legislation and Science

Legislation

US	Medical devices Medical Device Amendments of FD&C	Human cells and tissues, or cellular or tissue-based products PHS/42 USC 264	Drugs Food, Drug, and Cosmetic (FD&C) act
EU	Medical devices 93/42/EEC	Advanced therapy medicinal products 1394/2007	Medicinal products 2001/83/EC
JAPAN	Medical Devices	Regenerative medicine products	Drugs
	Pharmaceuticals, Medical Devices (PMD) act		

Science



Modified the EMA's presentation slide

Autologous hCTPs

JACE

2007

Japan

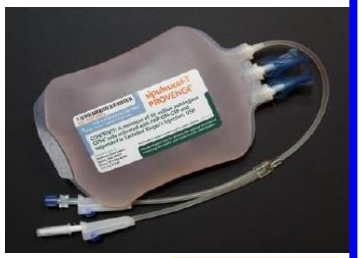
JACC

2012

Epicel®

2007

Provenge®



2010

US

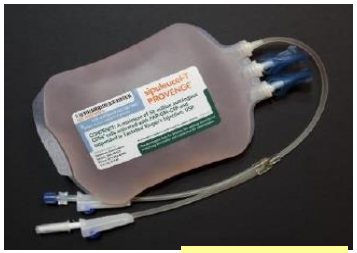
Carticel™

1997

Laviv™

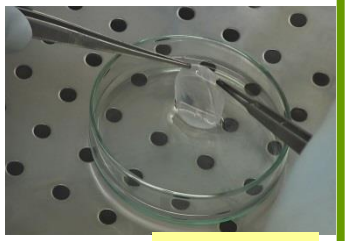
2011

Provenge®



2013

Holoclar®



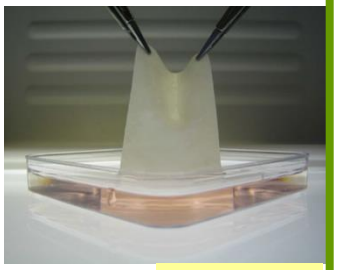
2015

EU

ChondroCelect®

2009

MACI®

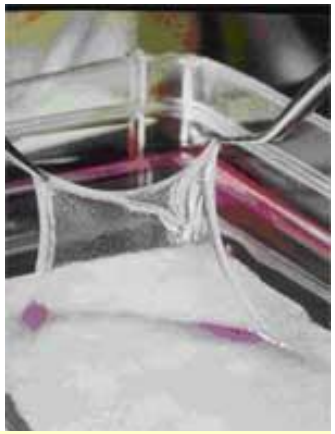


2013

Autologous hCTPs

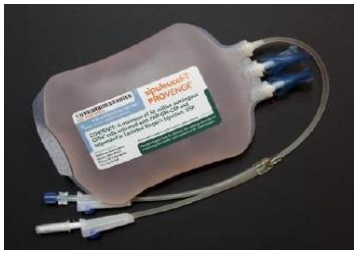
JACE

Epicel®

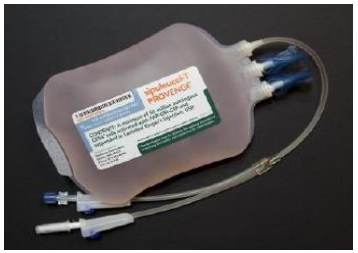


Deep dermal and full-thickness burns (greater than 30%)

Provenge®

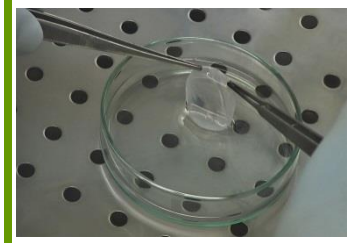


Provenge®



Asymptomatic or minimally symptomatic metastatic hormone refractory prostate cancer

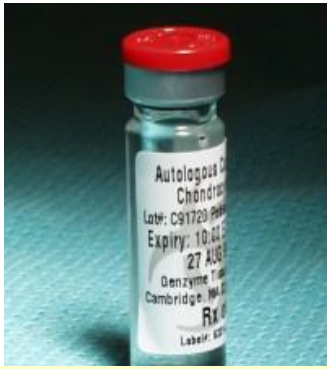
Holoclar®



Moderate to severe limbal stem-cell deficiency

JACC

Carticel™



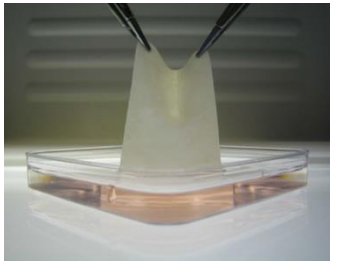
Cartilaginous defects of femoral condyle

Laviv™

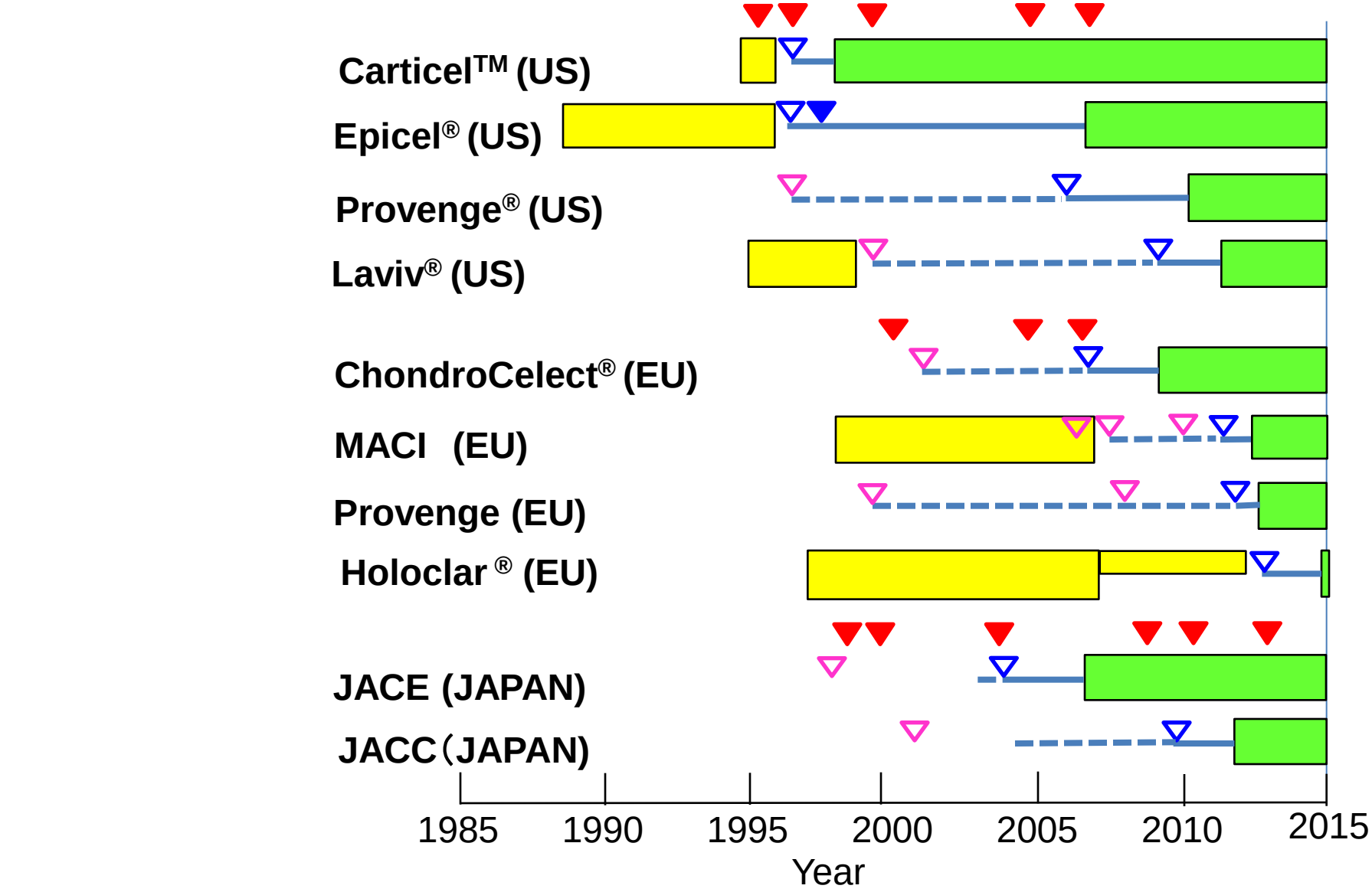
Nasolabial fold winkles

ChondroCelect®

MACI®



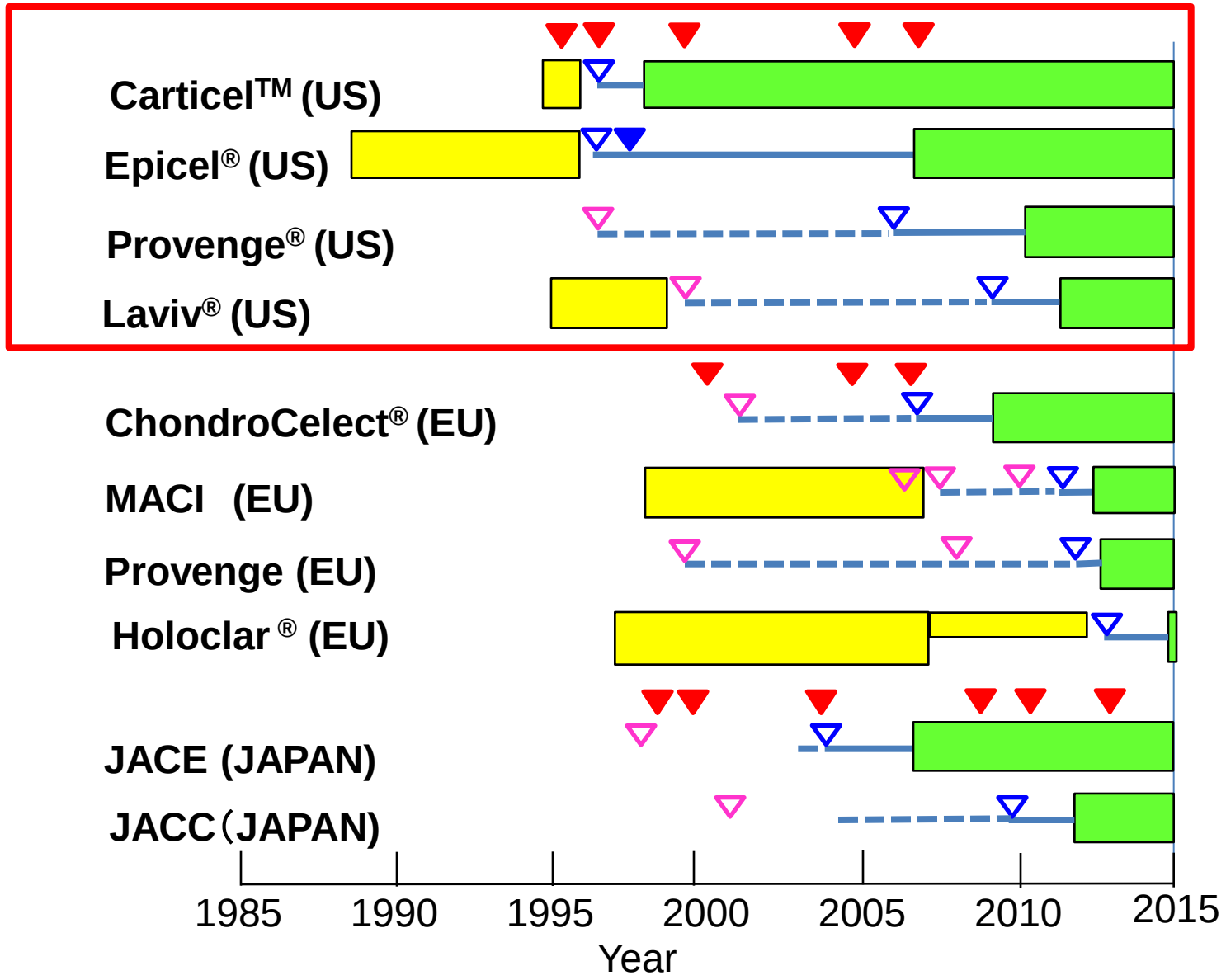
Cartilaginous defects of femoral condyle


Carticel™ (US)
Epicel® (US)
Provenge® (US)
Laviv® (US)
ChondroCelect® (EU)
MACI (EU)
Provenge (EU)
Holoclar® (EU)
JACE (JAPAN)
JACC（JAPAN)
1985
1990
1995
2000
2005
2010
2015
Year
Market prior to premarketing authorization
Market after premarketing authorization
Issuance of relevant regulation and guidance document
Submitted premarket application
Files as HUD
Submitted IND or confirming application, or registered to Clinical Trial.gov
Conducting clinical trials
Regulatory reviewing

Supplied as cell bank

Issued the first guidance manipulated autologous structural (MAS) cells products in 1996

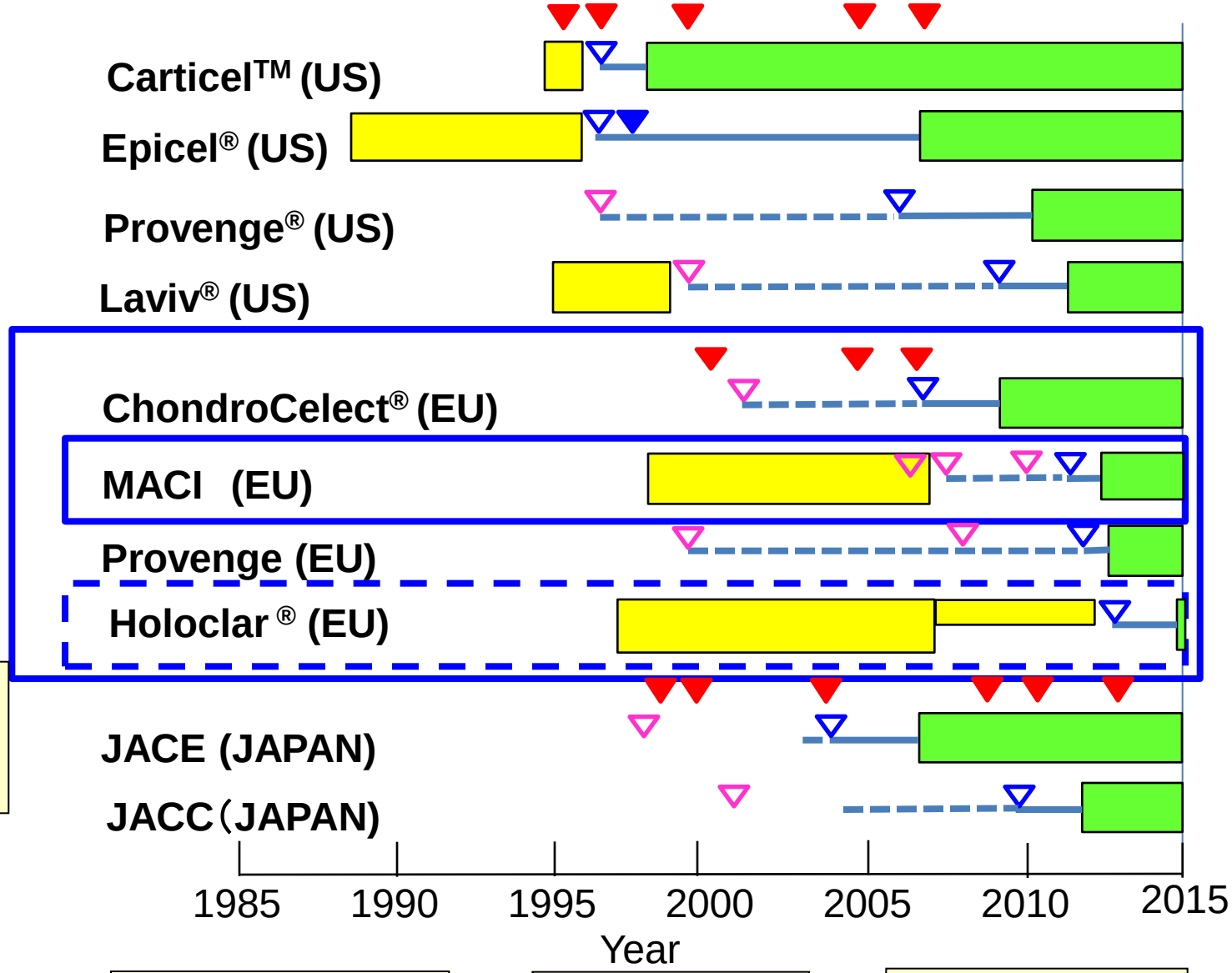
Submitted BLA, or conducted the clinical trials



MACI: On the market in Austria, Belgium, Demark, Germany, et. al., in 1998

Issued ATMP regulation in 2007

Applied central market authorisation



Retrospective evaluations in Italy (1998-2007; 2008-2013)

Designated as orphan medicinal product in 2008

Issued ATMP regulation in 2007

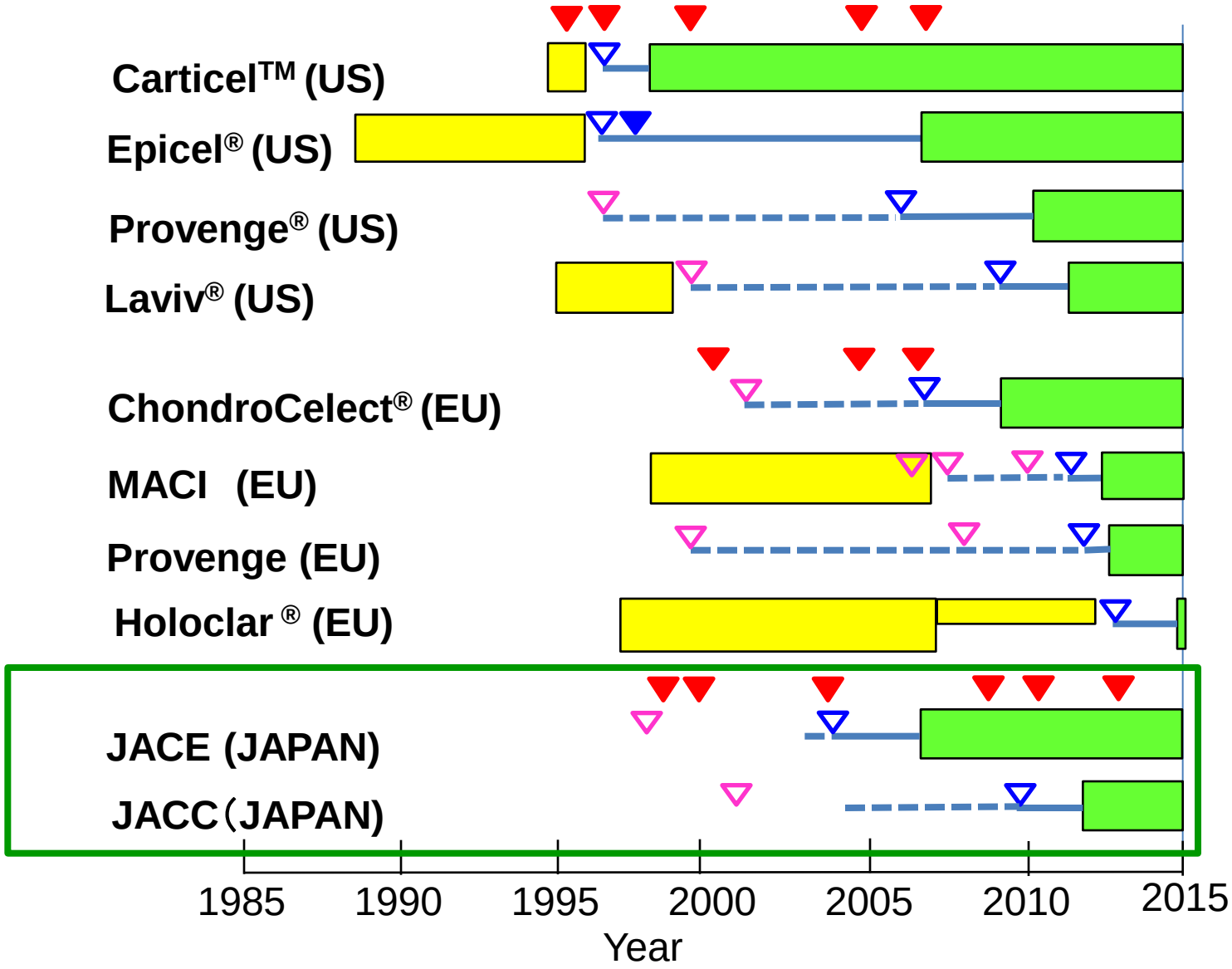
Holoclar ®: Treated at two sites in Italy (1998-2007)

registered to Clinical Trial.gov

Confirmatory application prior to conducting clinical trials in 1999

Content of confirmatory application in 2000

Rescinded confirmatory application in 2011



Market prior to premarketing authorization
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Files as HUD
Submitted IND or confirming application, or registered to Clinical Trial.gov
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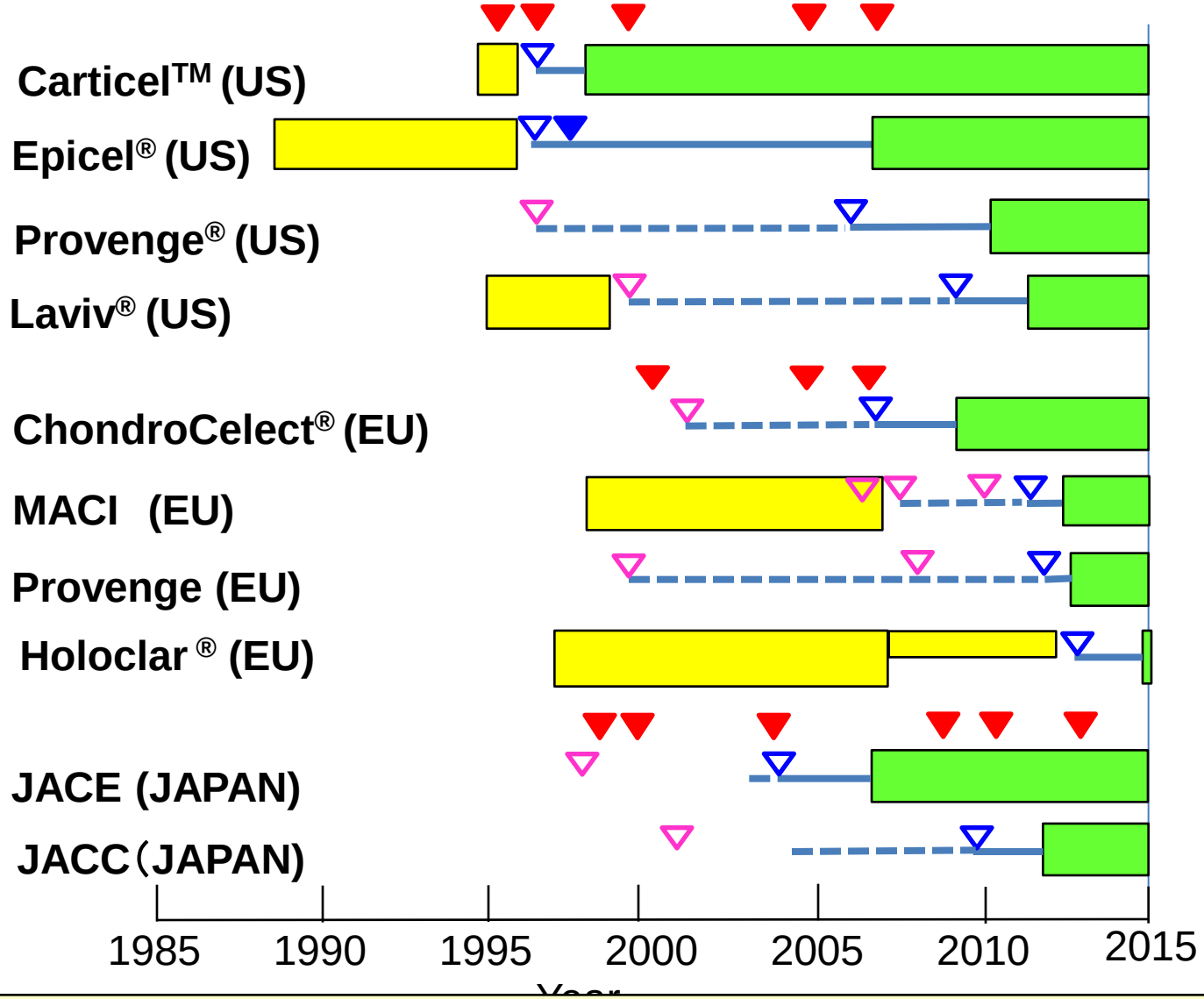


- **Issued regulation and guidance documents**

✓Accelerated approval as biologics, Humanitarian use exemption (HDE) as medical device, Biologics license approval (BLA), Premarket authorization as ATMP, Premarket approval as medical device, Conditional marketing authorization

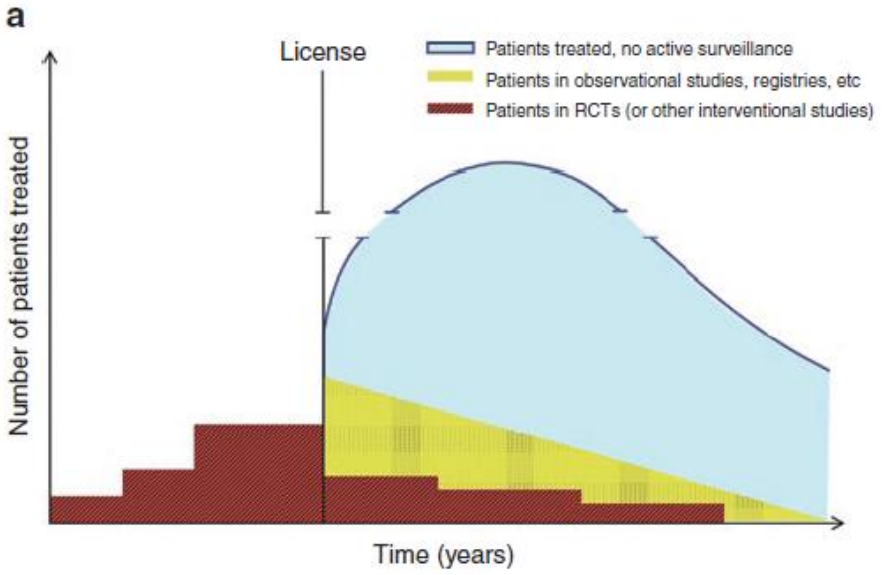
Safety and efficacy evaluation of autologous hCTPs

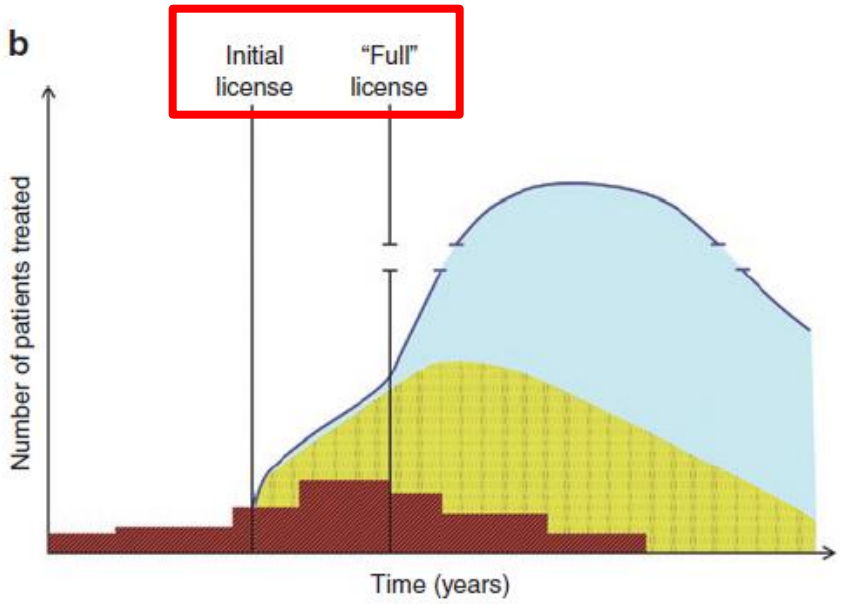
Trade name	Preapproval evaluation	Postapproval evaluation
Carticel™	**Nonclinical studies** •Rabbit studies of improved healing at 52 weeks •Dog study of improved healing at 13 and 26 weeks	**Nonclinical studies** •Goat studies of histological healing at 16 weeks •Horse study of histological healing at 8 weeks
•Swedish clinical experience: 153 patients •US registry: 191 patients	**Clinical studies** •Swedish clinical experience of 153 patients with retrospectively generated CRF •US registry data of 191patients repairing of femoral condyle in 241 patients treated	**Clinical studies** •Registry-base study (RBS) of 97 US patients •Study of the treatment of articular repair (STAR) of 154 patients: 136 patients at 24weeks and 115 patients at 48 months

- Of 10 autologous hCTPs, 5 products had been evaluated using clinical experiences or open clinical trials with small subjects
- Autologous hCTPs would need postmarket-oriented evaluation rather than premarket-oriented evaluation

Adaptive Licensing (concept)

Apply to drugs intended to severe or life-threating diseases or conditions





Existing approval system

Adaptive Licensing
- Initial license
- "Full" license

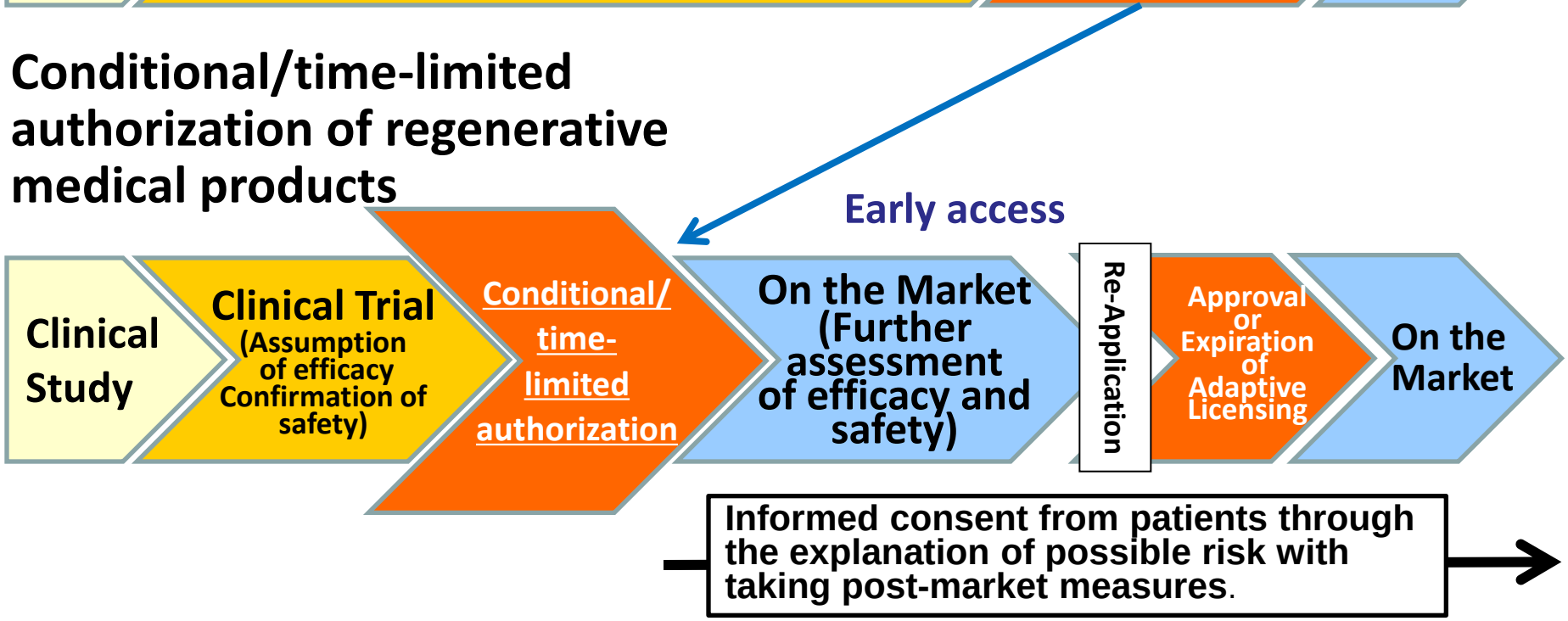
Extensive concept included "Accelerated Approval" in the US and "Conditional Marketing Authorization" in the EU

Eichler HG et al. Clin. Pharmacol. Ther. 2012;91:426-437

Newly introduced approval system for regenerative products in Japan

Current approval system

Conditional/time-limited authorization of regenerative medical products



Access URL：http://www.pmda.go.jp/guide/hyougikai/25/h250610kyusai/file/shiryo4-1.pdf (in Japanese)

Post-market registry and surveillance of autologous hCTPs

Trade name	Post-market clinical evaluations
Carticel™	Post-market study and CRT
Epicel®	HDE (Ethical committee review before clinical use)
Provenge®	1,500-patient registry
Laviv®	2,700-patient registry (possibility of skin cancer)
ChondroCelect®	Post-market safety and efficacy study
MACI®	Post-market safety and efficacy study
Holoclar®	Prospective interventional study (conditional market authorization)
JACE	Post-market surveillance of all patients for seven years
JACC	Post-market surveillance of all patients for seven years

- After premarket approval, post-market registries and surveillances have been conducted according to the condition of approval

Autologous hCTPs: Recalls

Trade name	Recall class and reasons
Carticel™	Class 2 : Possible contaminated with *Novosphingobium capsulatum* (2006/5/17) Class 2: Revised labeling of essential kit clarifies the non-sterile packaging of the out clear plastic tray (2010/9/1)
Epicel®	Not available (NA)
JACE	NA
ChondroCelect®	NA
Provenge®	Class 3: Manufactured with a breach of disposal collection kit, was distributed (2012/4/25)
Laviv®	NA
MACI®	NA
JACC	NA

- Recalls for two autologous hCTPs (Carticel™, Provenge®) were enforced three times

Summary of autologous hCTP

- Approved ten autologous hCTPs (4 products in the US; 4 products in the EU; 2 products in Japan)
- Occurred a significant regulatory impact in 1996 in the US, when the first guidance was issued
  - ✓ Accelerated approval of biological products, Humanitarian use device (HUD)/Humanitarian device exemption (HDE); Biological license application approval (BLA)
- Of ten products, five were approved using clinical data such as clinical experiences, small subjects, approval with conditions (Carticel™, Epicel®, JACE, JACC, Holoclar®)
- The rest of products were approved using clinical data of controlled randomized trials (CRTs: Provege®, Laviv®, ChondroCelect®, MACI)
- Enforced 3 recalls for two autologous hCTPs (Carticel™, Provenge®)
- Notified 63 adverse event reports for Epicel® (3 serious adverse events related to use Epicel®)

Conclusions

- The clinical evaluation of autologous hCTPs would focus on postmarket-oriented evaluation rather than premarket-oriented evaluation.
- We should consider that the premarket clinical evaluations of these products need to use not only clinical experience but also historical control data, and to use adaptive licensing for approval system.

Regenerative Therapy 1 (2015) 45–56

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journal homepage: http://www.elsevier.com/locate/reth

Regulatory approval for autologous human cells and tissue products in the United States, the European Union, and Japan

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[a] Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-866, Japan
[b] Research Institute for Science and Engineering, Waseda University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-866, Japan
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Biologicals xxx (2015) 1–15

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journal homepage: www.elsevier.com/locate/biologicals

Meeting report

Report of the international conference on regulatory endeavors towards the sound development of human cell therapy products☆

Takao Hayakawa [a], Takashi Aoi [b], Christopher Bravery [c], Karin Hoogendoorn [d], Ivana Knezevic [e], Junichi Koga [f], Daisuke Maeda [g], Akifumi Matsuyama [h], James McBlane [i], Tomohiro Morio [j], John Petricciani [k, *], Mahendra Rao [l], Anthony Ridgway [m], Daisaku Sato [g], Yoji Sato [n], Glyn Stacey [o], Norihisa Sakamoto [g], Jean-Hugues Trouvin [p], Akihiro Umezawa [q], Masayuki Yamato [r], Kazuo Yano [r], Hiroyuki Yokote [s], Kentaro Yoshimatsu [f], Pierrette Zorzi-Morre [t]

Commentary of Chemotherapy

Diverse approval systems for autologous human cells and tissue products

Kazuo Yano[1,2,3], Natsumi Watanabe[1,3], and Masayuki Yamato[1,3]

Accepted on August 21, 2015.

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4th Annual Conference on European Pharma Congress

June 18-20,2016, Berlin, Germany.

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