PMDA 4th International Symposium on Biologics

J-TEC's perspective:

The clinical development of the autologous cell/tissue-based medicinal products

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Transition in study of Regenerative Medicine in Japan

- 1981　Clinical Application of Cultured Epidermis
- 1980 - early 90's
  Development of Medical Treatment using human tissue under medical practitioners law
- 1990 – 2000
  - Beginning of new era of "Tissue Engineering" (1993) and "Regenerative Medicine"
  - "Medical Investigation" ≒ "Regenerative Medicine"
  - Kyoto University's Institute for Frontier Medical Sciences (since 1998)

Established J-TEC

  - "Millennium Project : national commitment " (1999) and University-launched Venture company
  - Issuance of MHLW Guideline of No.1314　(2000)

Transition in study of Regenerative Medicine in Japan

- Big wave of Bio-tech Business including the field of Regenerative Medicine
  - "Major Plan for Development of New Industry and Job Creation" (2001)
  - Institute of Biomedical Research and Innovation (IBRI) in Kobe (since 2003)
- Discussion of CPC at the university
  - Proposal of iGMP
- Sept. 1st, 2006
  - Issuance of Guideline of treatment for human stem cell
- Establishment of preparing human iPS cells (2007)
- Revision of MHLW Guideline of No.1314 (2008)

Autologous Cultured Epidermis

1975 : Prof. H. Green of Harvard Medical School developed a method that involved culturing keratinocytes together with mouse fibroblasts to form a keraninocyte sheet, a method known as Green's technique for culturing epidermis.

- Rheinwald JG, Green H : Serial cultivation of strains of human epidermal keratinocytes: the formation of keratinizing colonies from single cells. *Cell* 6 : 331-344 (1975)
- Green H : Cyclic AMP in relation to proliferation of the epidermal cell: a new view. *Cell* 15 : 801-811 (1978)

1981 : World first report: Grafting Green-type autologous cultured epidermis (ACE) for the treatment of severe burn patients (First case of medical treatment of TEMPs)

- O'Connor NE, Gallico GG, Compton CC, Kehinde O, Green H : Grafting of burns with cultured epithelium prepared from autologous epidermal cells. *Lancet* 1 (8211) : 75-78 (1981)

1984 : The lives of two severely burned children were saved by Green-type ACE cultured from 2 cm^2 skin remained to them.

- Gallico GG III, O'Connor NE, Compton CC, Kehinde O, Green H : Permanent coverage of large burn wounds with autologous cultured human epithelium. *N Engl J Med* 311 : 448-51 (1984)

1985 : Japan first report: Green-type ACE were used for the treatment of severe burn patients in Japan by Prof. N. Kumagai of St. Marianna University of Medicine.

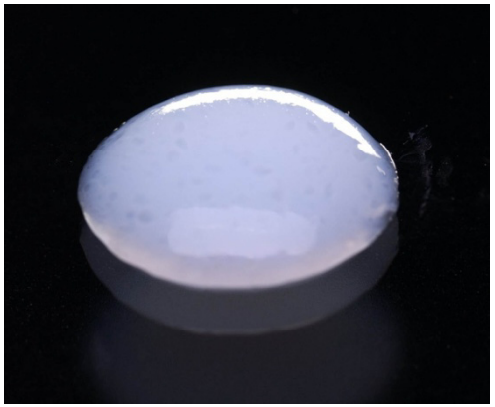
- Kumagai N, Nishina H, Hosaka T, Ogino Y: A study of human cultured epidermis, Japanese J Prast. Surg. 5:463-474(1985)

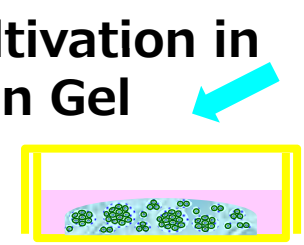
Indications of Cultured Epidermis

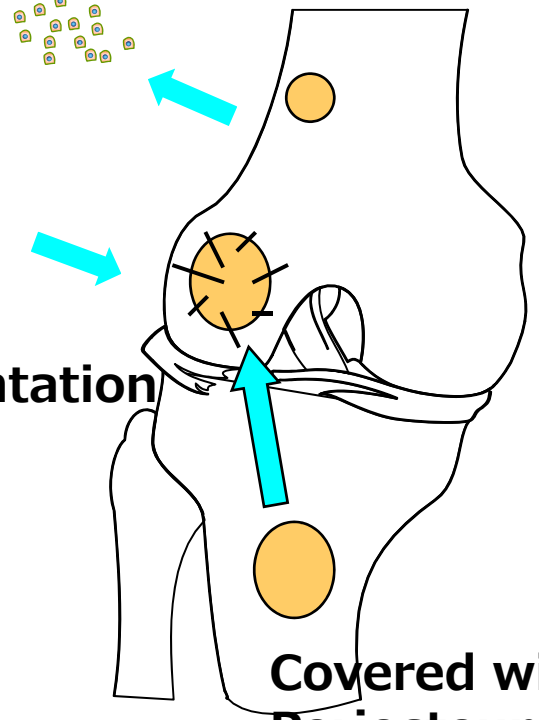
etc….

Tissue-Engineered Cartilage

Prof. Ochi (Hiroshima University)







- Improve inadequacies of ACI technique by 3-D Cultivation (prevent de-differentiation of chondrocytes and retain their phenotype)
- Existence of chondrocytes having proliferation potency
- Production of cartilage matrices

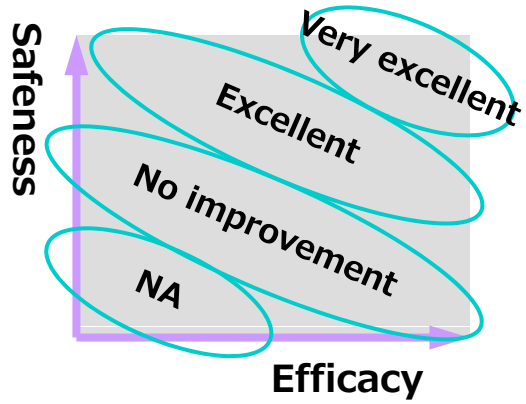
Cartilage – Result of Clinical Trial

- About 40 patients participated in the clinical trial. J-TEC monitored their results after surgery for 1 year.

[Patient]

- Elbow)Chef
- Elbow)Building constructor
- Knee) Physical education teacher
- Knee) Farmer
- Knee) 68 year-old senior
- Knee) 120kg weight female
- Knee) Aerobics instructor
- Knee) Nurse

[Result]



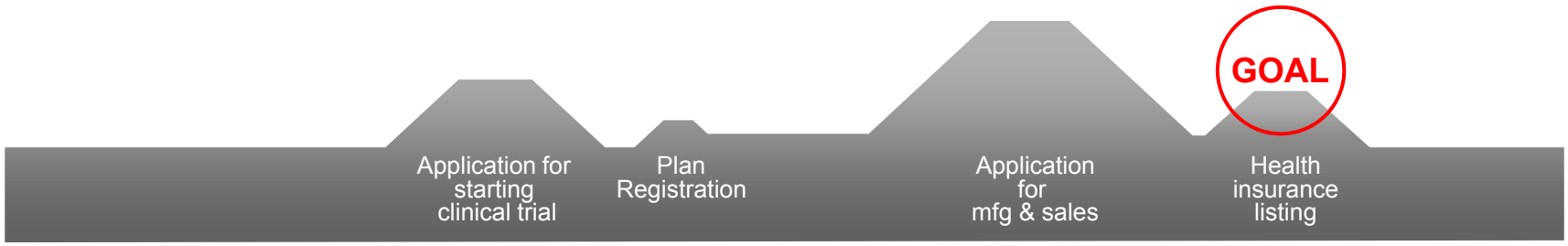
HQ and Approved GMP Facilities

- J-TEC is the only bio-tech company in Japan with approved GMP facilities.

Foundation:	Feb.1, 1999
HQ location:	Gamagori
Capital:	5,553 mil yen
Employee:	117

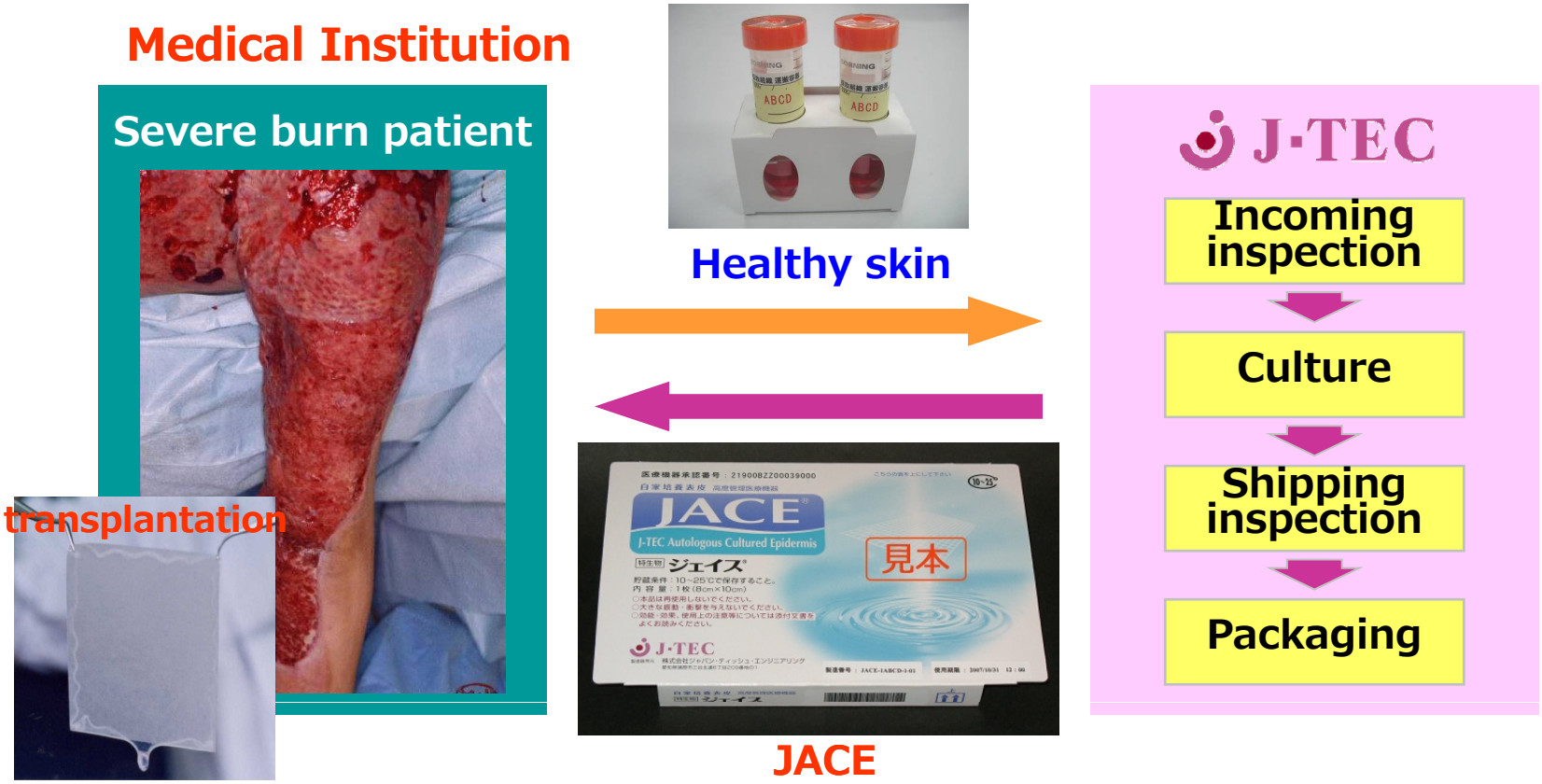
Regulation for cell/tissue-based medicinal products

- Japanese pharmaceutical law "Yakuji-ho" requires TE & RM products an extra-step of application for starting clinical trial.



JACE Business Model

- From a stamp-sized sample of a patient's own healthy skin, J-TEC cultures enough epidermis to cover the patient's entire body within 3 weeks.



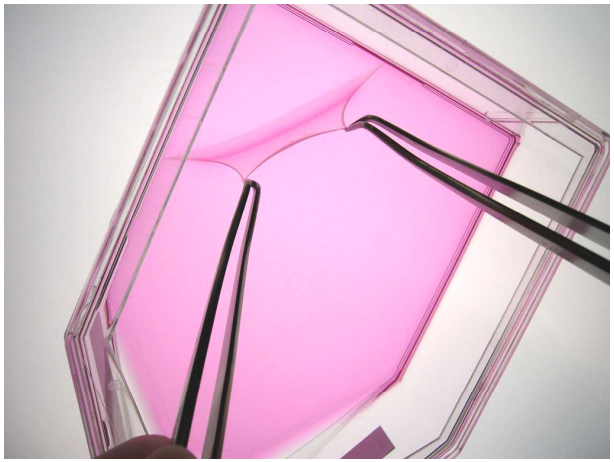
Autologous Culture Epidermis JACE

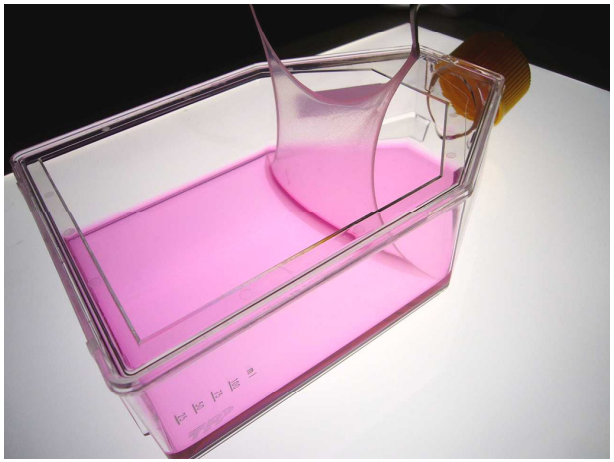
JACE®
J-TEC Autologous Cultured Epidermis

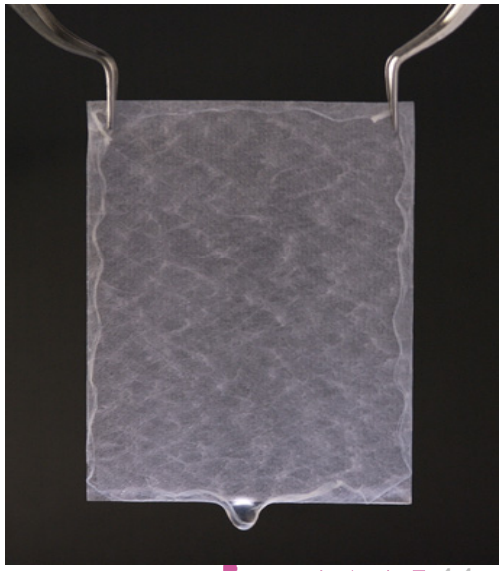
Approval code:
21900BZZ00039000

- JACE, J-TEC's Autologous Cultured Epidermis is a keratinocyte sheet cultured together with 3T3-J2 cells (derived from mouse) as feeder cell, and FBS.
- JACE is a skin-like sheet with the keratinocyte and it is strength enough to suspend with career sheet.

【Indication】 Severe burn; DDB + DB >= 30%

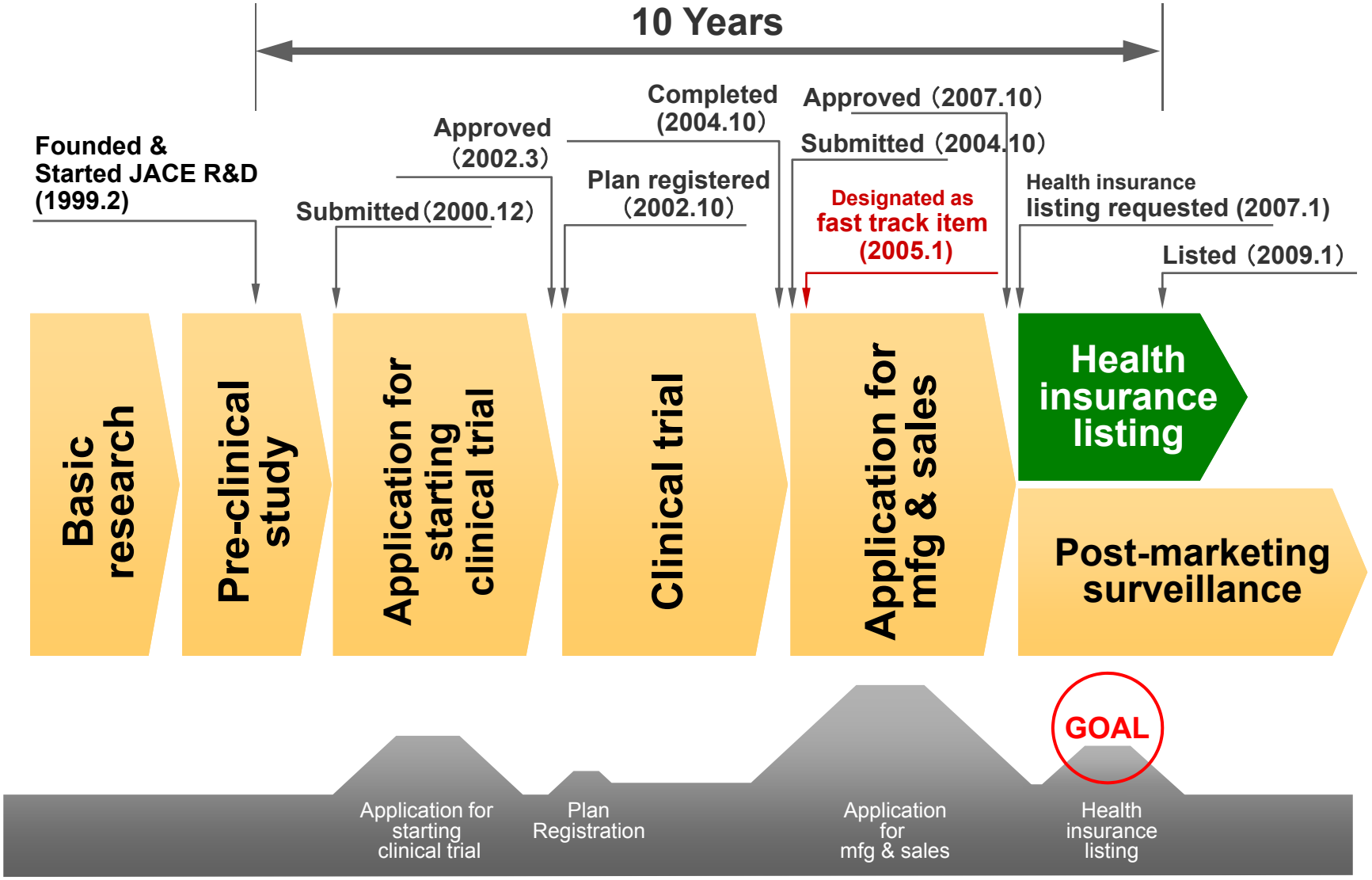




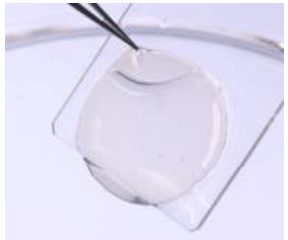


Autologous Culture Epidermis JACE

10 Years to Launch



Pipelines

	Autologous Cultured Epidermis	Autologous Cultured Cartilage	Autologous Cultured Corneal Epithelium
Product outlook			
Alliance	Prof. Howard Green, Harvard Univ., USA	Prof. Mitsuo Ochi, Hiroshima Univ., JP	Veneto Eye Bank, IT Prof. Michele De Luca & Prof. Graziella Pellegrini, Modena Univ., IT
Business territory	Japan	Worldwide	Asia
Indication*	Severe burn: DDB + DB >= 30%	- Traumatic cartilage deficiency -Osteochondrosis dissecans -Osteoarthrosis	-Chemical burn -Stevens-Johnson syndrome -Relapsed pterygium -Pemphigus, others
Reg. status	(Manufacturing & Sales) Approved Oct. 2007 (Health Insurance) Listed Jan. 2009	Submitted an application for mfg & sales, Aug. 2009	Submitted an application for starting clinical trial

*Indication for autologous cultured cartilage & corneal epithelium: J-TEC's Projection.

Approval for Starting a Clinical Trial

Products	Category	Company	Approval date	Status
Immuno-therapy for cancer by dendric cells	Drag	KYOWA HAKKO KIRIN KYOWA KIRIN	2001.10	Suspended
Cultured epidermis	Medical Device	J-TEC J·TEC	2002.03	Approved for M&S (2007.10)
HGF gene therapy	Drag	Anges MG Anges	2003.10	Submitted application for M&S (2008.03)
Cultured cartilage	Medical Device	J-TEC J·TEC	2004.02	Submitted application for M&S (2009.08)
Heart regeneration by myobrast	Drag	TERUMO TERUMO	2006.04	Preparing for clinical trial
Treatment for GVHD by MSC	Drag	Japan Chemical Research JCR	2007.05	Preparing for clinical trial
HSV-TK gene therapy	Drag	TAKARA BIO TaKaRa	2007.09	Preparing for clinical trial
FGF gene therapy	Drag	Sanofi-aventis sanofi aventis	2007.11	Preparing for clinical trial
Cultured skin	Medical Device	BCS BCS	2007.12	Preparing for clinical trial
Cultured corneal epithelium	Medical Device	Arblast ArBlast	2009.06	Preparing for clinical trial

TEMPs has less products/experiences than Pharmaceutical/Medical device industry

Safety

Efficacy

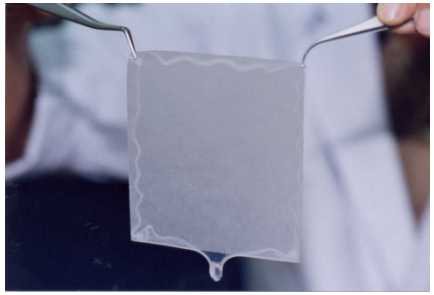
Concreteness

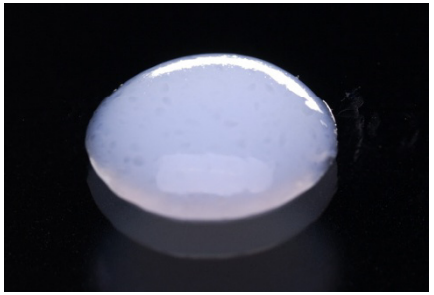
Uniformity

Reality

Consistency

The Aim of Autologous Cell Therapy



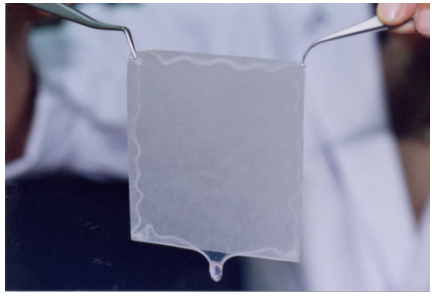


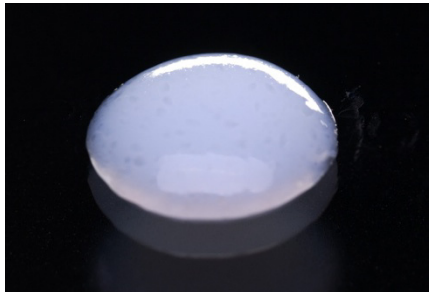
- Recovery from previously untreatable disorders
- Minimized physical strain of patient
- Avoiding uncertainty of treatment and operation

Evaluation of Safety and Efficacy

How do you know it's safety?

- No infectious factor such as pathogenic organism
- No anticipated immune reaction such as allergy
- No risk of transformation after grafting





Objective evaluation of TEMPs

How do you know it's efficacy?

- Efficacy of the treatment
- Efficacy of the product

Japanese Guideline on Autologous Human Cell-based Medicinal Products

Chapter 7 Clinical trial

On application for starting clinical trial, the safety should be evaluated under considerations of clinical usefulness, and the design of domestic clinical trial for cell-based medicinal products also should be evaluated about the point as mentioned below.

1. Indication
2. Inclusion criterion and exclusion criteria in treatment protocol
3. Therapeutic regimen
4. Adequacy for clinical trial
5. Assumed risks and benefits, content of informed consent

Guideline on Ensuring Quality and Safety of Products Derived from Processed Human (autologous) Cells/Tissues
(MHLW Notification No. 0208003 8 Feb. 2008)

Dilemma of Clinical Studies using autologous tissue

- **Primary Endpoint**
  - **Clinical improvement vs. Histological regeneration**
    No objective indication such as clinical test values
- **Evaluation method**
  - **Established method vs. Original method**
    Few established method, because Regenerative Medicine is the novelty field
- **Controlled trial / Blind trial**
  - **Are Controlled trial and Blind trial actual?**
    Because of the surgical operation, it's difficult to set the control group and blind trial.
- **Stratified analysis**
  - **How to do stratified analysis? How to set appropriate indication?**
    Difficult to justify the classification for stratified analysis
    Limited cases

Controlled Trial / Blind Trial

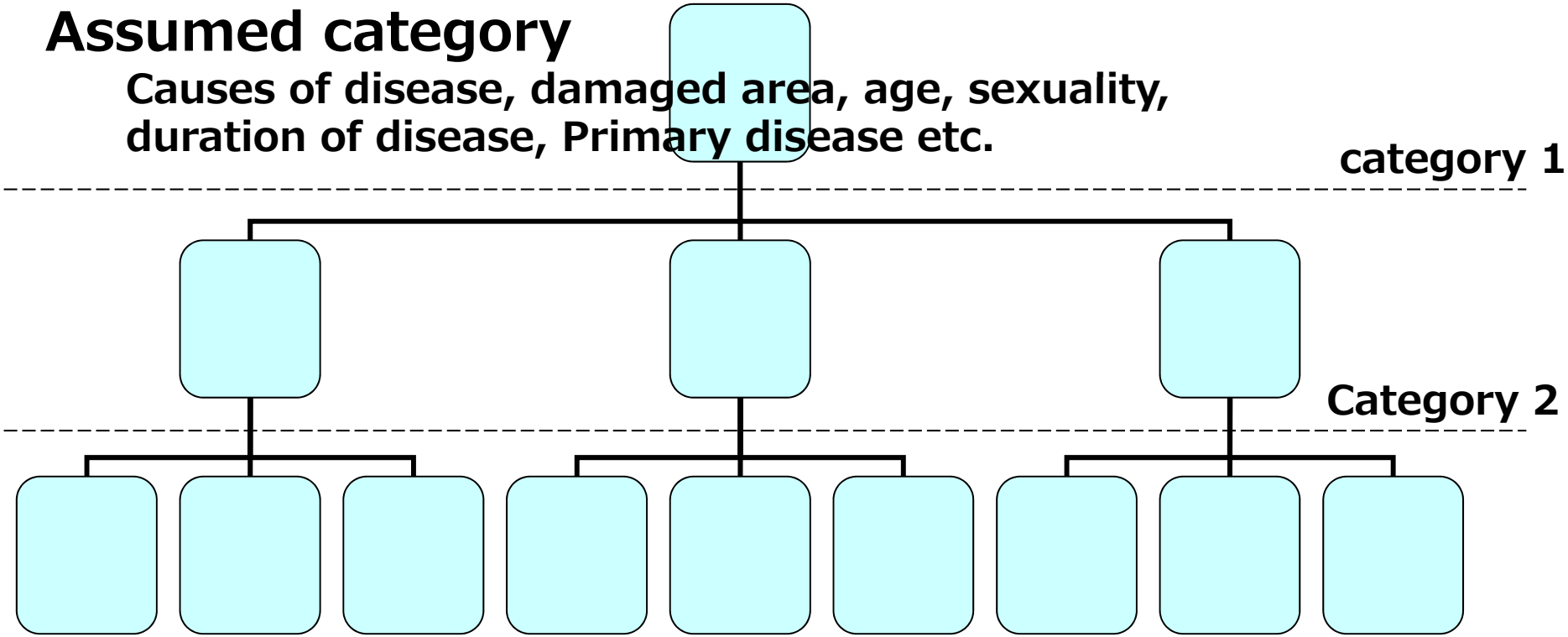
- **Microfracture**
  - Palliative treatment: Aiming short-term improvement by restoration of cartilage. Its performance and limitation are well-known.
  - Ethical adequacy of invasive examination such as arthroscopy or biopsy as controlled trial.

JACC	Microfracture
Arthroscopic biopsy	Equivalent procedure losses the blindness
Grafting ・Open Surgery	Operation ・Arthroscopy (loss the blindness, discrepancy of operation scale) ・Open Surgery (ethical issue)
Follow-up assessment ・Arthroscopy ・Biopsy	Follow-up assessment ・Arthroscopy (ethical issue) ・Biopsy (ethical issue)
	Necessity of Retreatment ・Negative impact of the treatment using cultured cartilage

Stratified analysis

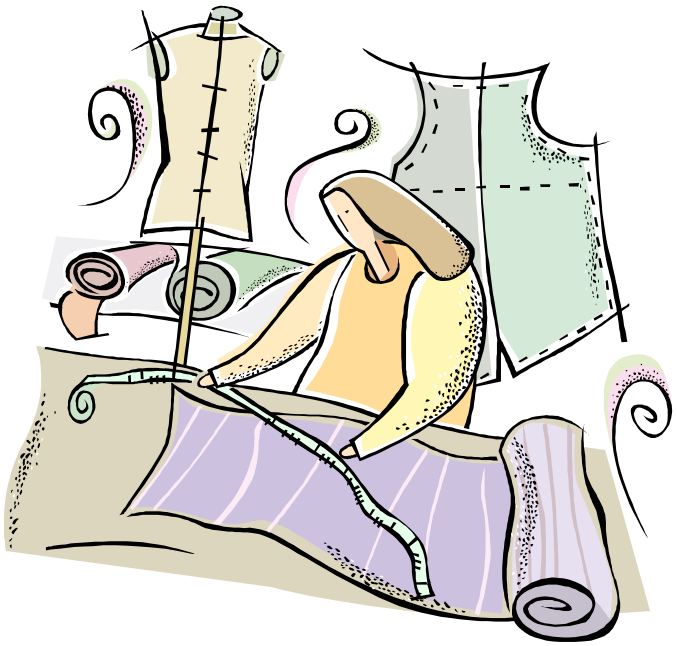
Assumed category

Causes of disease, damaged area, age, sexuality, duration of disease, Primary disease etc.



Tasks of categorization by background factor

- No rational marker of categorization
  (Level of details for analyze the categorization)
- Meanings of categorization for efficacy evaluation not for safety evaluation.
- Depending on operative procedure, background factor might not be disclosed.

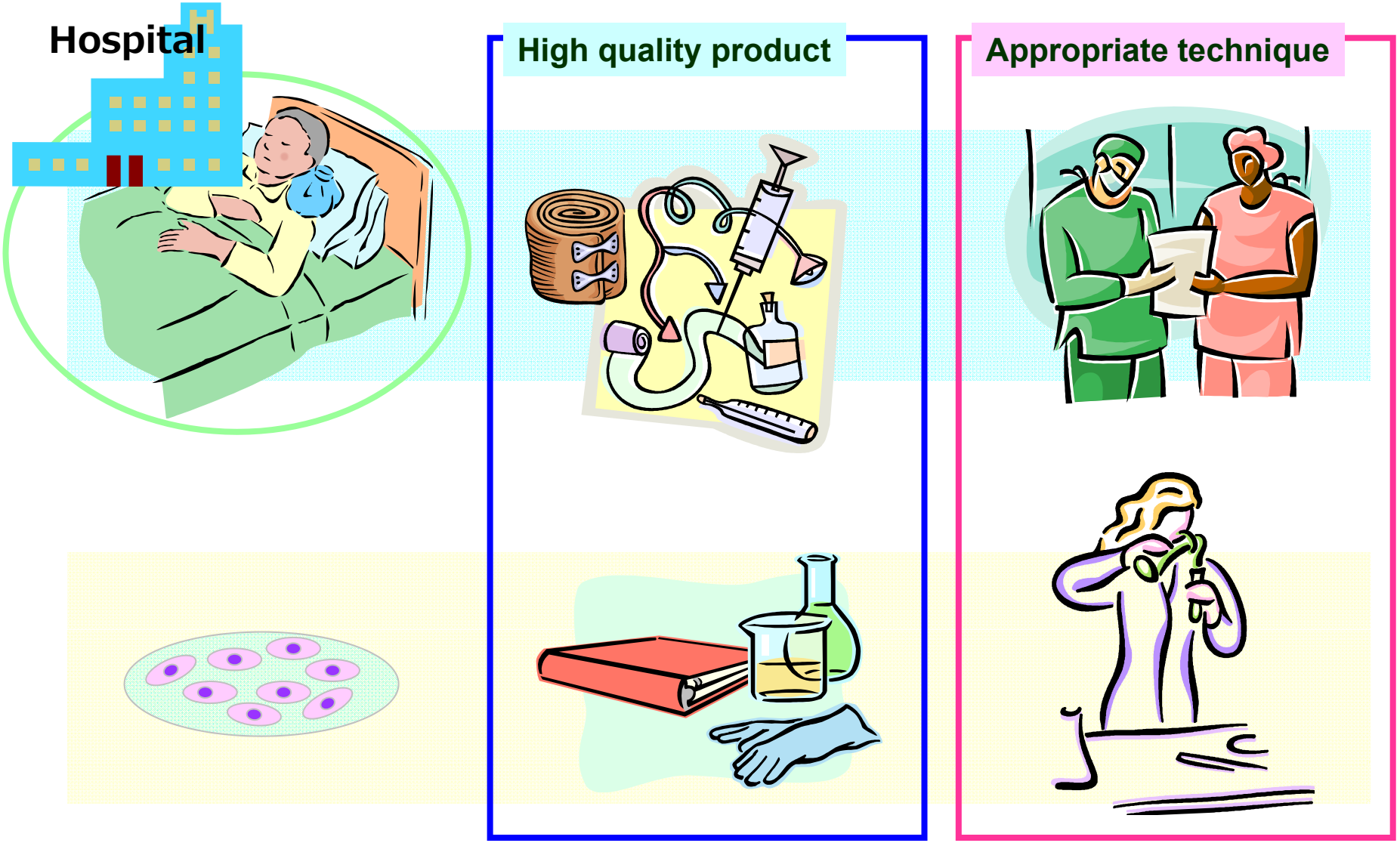


Boutique

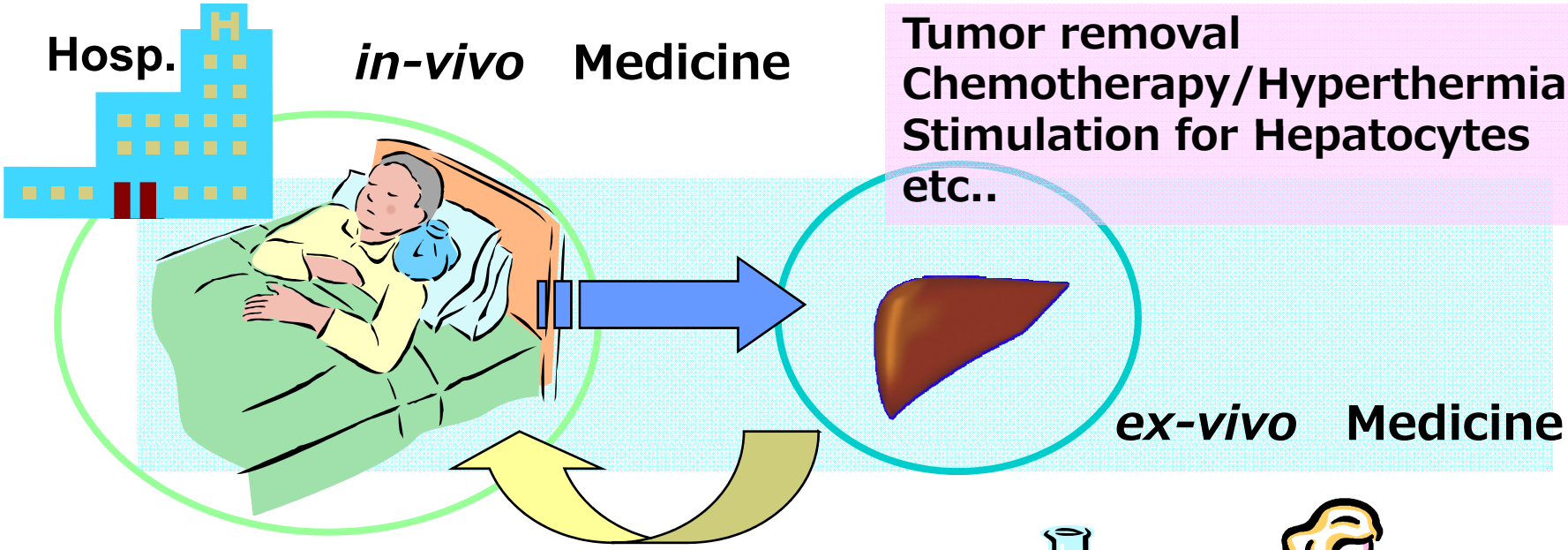
Manufacturer of pharmaceutical products/medical devices/TEMPs using allogeanic tissues

Laundry

Manufacturer of TEMPs using autologous tissues


Hospital
High quality product
Appropriate technique

From Human Treatment to Organ Treatment.



- ◆preservation/restoration *ex-vivo* technique of tissue or organ
- ◆techniques of substitutional artificial organ
- ◆grafting technique etc.

Reimbursement policy of JACE

【facility criterion 】

Institute that has special intensive-care unit (ICU) for burn care.

notification (24*1)	reimbursement	No reimbursement
Not notification (150)	No reimbursement	No reimbursement

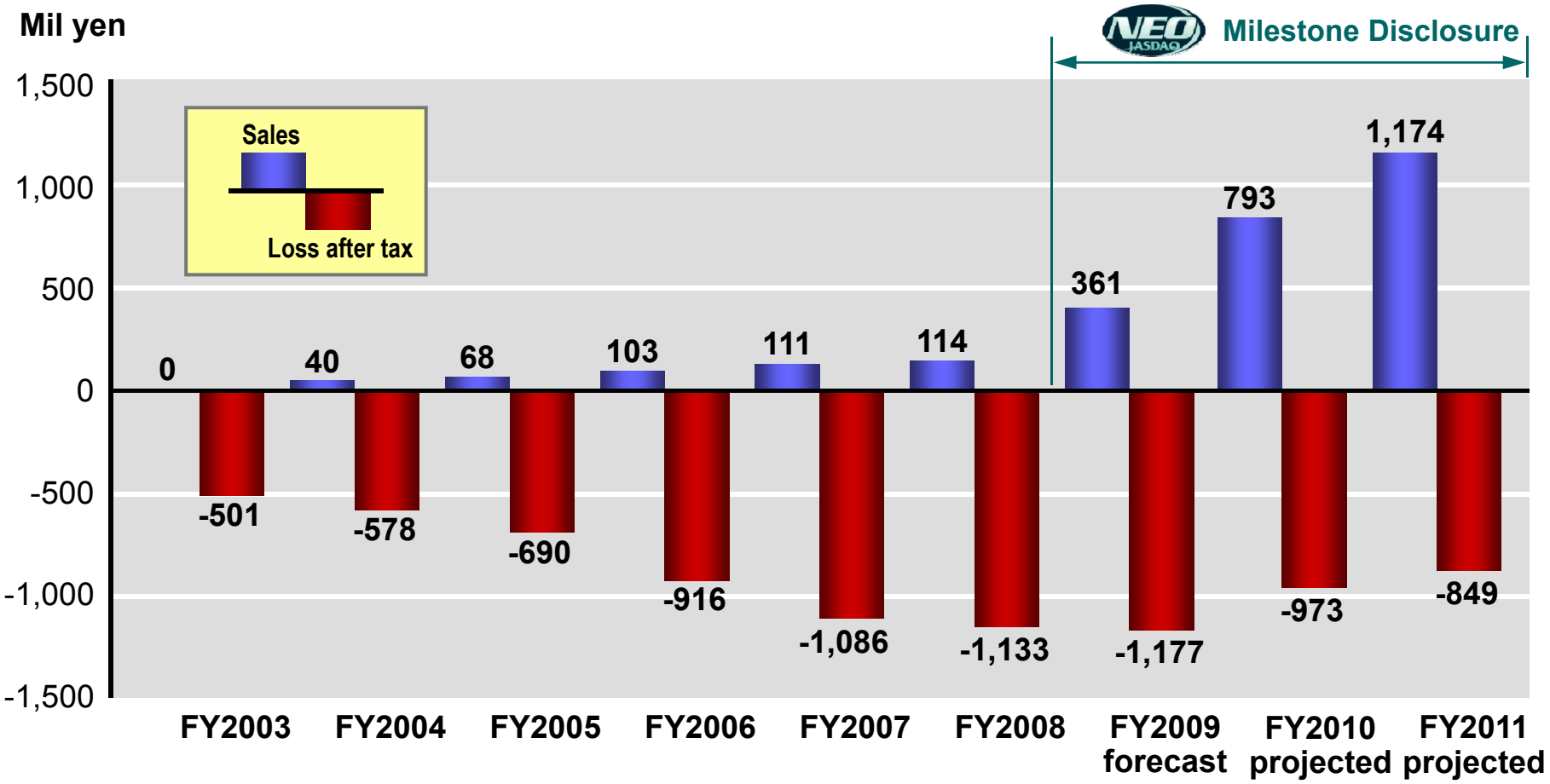
1～20 sheets ⟷ More than 21 sheets
Supplying for one patient

【Reimbursement limits】
20 sheets are limits

*1: Hokkaido 0、Tohoku 3、Kanto 9、Chubu 5、Kinki 5、Chugoku 0、Shikoku 1、Kyushu 1
(1 Oct 2009)

Profit and Loss

- The launch of autologous cultured cartilage (JACC) is projected in FY2011.



Experience

is important to make the guideline for safety.

Thank You!

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