Report on the Deliberation Results

November 21, 2018

Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Classification	Human cellular/tissue-based products, 1 Human somatic cell-processed products
Non-proprietary name	Human (autologous) epidermal cell sheet
Brand name	JACE
Applicant	Japan Tissue Engineering Co., Ltd. (J-TEC)
Date of application	March 20, 2018 (partial change approval application)

Results of deliberation

In its meeting held on November 21, 2018, the Committee on Regenerative Medicine Products and Biotechnology made the following decision and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

This application may be approved. The re-examination period is 10 years.

The following conditions of approval should be imposed.

Conditions of approval

1. Because the clinical studies were conducted in extremely limited number of subjects, the applicant is required to conduct a use-results survey covering all patients treated with the product. As a rule, the survey should be continued until the end of the re-examination period. New efficacy and safety data on the product should be communicated appropriately to surgeons/physicians and medical institutions providing treatment with the product, and patient information materials should be updated with the data accordingly.
2. Due to the risks associated with xenotransplantation of 3T3-J2 cells derived from mouse embryo, which are used as feeder cells in the manufacture of the product, the applicant is required to take necessary measures to ensure appropriate handling, such as 30-year retention of a sample of the finished product and a record of use.

Review Report

November 5, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following regenerative medical product submitted for partial change approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand name	JACE
Classification	Human cellular/tissue-based products, 1 Human somatic cell-processed products
Non-proprietary name	Human (autologous) epidermal cell sheet
Applicant	Japan Tissue Engineering Co., Ltd. (J-TEC)
Date of application	March 20, 2018
Shape, Structure, Active Ingredient, Quantities, or Definition	An epidermal cell sheet supplied in the package for cultured epidermis is "autologous cultured epidermis" produced from keratinocytes isolated from a patient's own skin tissue. The isolated keratinocytes are cultured into cell sheets for autografting. Cultured (autologous) epidermal cell sheets are grafted onto the wound surface with preserved dermis for the closure of the wound via engraftment/epithelialization. Each container for cultured epidermis contains 1 piece of cultured epidermal cell sheet. A tissue transport tube is used to store and transport the harvested tissue.
Application Classification	(3) Regenerative medical product with a new indication
Items Warranting Special Mention	Orphan regenerative medical product (Orphan Device Designation No. 22 of 2011 [*23 ki*]; PFSB/ELD/OMDE Notification No. 0318-2 dated March 18, 2011, issued by the Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of Cellular and Tissue-based Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in patients with dystrophic epidermolysis bullosa and is expected to have efficacy in patients with junctional epidermolysis bullosa, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication or performance and dosage and administration or method of use shown below, with the following conditions.

Indication or Performance

1. Severe burns

JACE is indicated for use in patients with serious, extensive burns when sufficient donor sites for autologous skin grafts are not available and the total area of deep dermal and full-thickness burns is 30% or more of the total body surface area. A cultured epidermal cell sheet is applied onto the reconstructed dermis in a full-thickness burn wound to facilitate the closure of the wound. Dermis should be reconstructed with allografts, as a general rule. JACE should be used for deep dermal burn wounds only when full-thickness and deep dermal burns coexist and it is difficult to treat them separately.

2. Giant congenital melanocytic nevi

The cultured epidermal cell sheet is applied onto a wound after excision of giant congenital melanocytic nevi to facilitate the closure of the wound.

3. Dystrophic epidermolysis bullosa and junctional epidermolysis bullosa

JACE is indicated for the treatment of intractable or recurrent erosions/ulcers in patients with dystrophic or junctional epidermolysis bullosa. The cultured epidermal cell sheet is applied onto an intractable or recurrent erosion/ulcer to promote epithelialization.

(Underline denotes additions.)

Dosage and Administration or Method of Use

Grafting plan

1. Grafting plan

A treating surgeon/physician develops a grafting plan and provides the manufacturer of JACE with the details of the plan, which consist of the number of cultured epidermal cell sheets required, the dates of tissue harvest and grafting, the number of grafting procedures, and other necessary information such as on the medical institution and the patient (hereinafter collectively referred to as the “grafting planning information”). The manufacturer prepares an order form indicating a tissue code unique to each grafting plan and the grafting planning information, then send it to the treating surgeon/physician.

The treating surgeon/physician confirms the grafting planning information entered in the order form sent by the manufacturer, before placing an order for production of JACE.

The manufacturer supplies the surgeon/physician with a tissue transport kit (comprising tissue transport tubes) and a dedicated heat-insulating container in time for the date of tissue harvest. The tissue code is indicated on the carton of the tissue transport kit, tissue transport tubes, and heat-insulating container for tissue transportation provided by the manufacturer.

Tissue code

Tissue codes are issued for each grafting plan.

For a patient undergoing tissue harvest more than once, each piece of tissue harvested is identified by a unique tissue code. A grafting plan is developed on a tissue-code basis.

For a patient undergoing a single tissue harvest followed by serial grafting procedures, cultured epidermal cell sheets for multiple grafting procedures are produced using cells derived from the same skin tissue. The tissue code remains unchanged for production of such sheets. Therefore, these sheets are identified with the same tissue code and different batch numbers.

Steps from tissue harvest at the medical institution through the receipt of harvested tissue

2. Tissue harvest

Skin tissue is harvested based on the size of the graft recipient site and according to the grafting plan. The harvested skin should be at least 1 cm^2 in size and elliptical in shape or in such a shape that allows for easier suture. Skin tissue is taken from lesion-free normal skin at any anatomical site. The full-thickness of dermis should be harvested from the donor site.

3. Storage of harvested tissue

The sealing band on the heat-insulating container is cut with scissors to remove the lid and take out the tissue transport kit. The tissue code indicated on the heat-insulating container, carton of the tissue transport kit, and tissue transport tubes is checked against the order form.

The tissue transport kit is unsealed in a clean environment (e.g., operating room, procedure room) to take out the transport tube. The tube is checked for leakage and turbidity of the medium filled in it. If the medium is turbid, the spare tube is used.

The tissue transport tube should not be tilted or shaken unnecessarily.

The tissue transport tube is uncapped. The skin tissue, harvested in a clean environment, is placed in the tube using sterile forceps, etc. to be immersed in the medium. The tube is then capped tightly to prevent a leak of the medium. The date of tissue harvest and the name of the person who performed harvest are indicated on the tube.

4. Transportation of harvested tissue

The tissue transport tube is placed in the carton. The carton is sealed for tamper resistance and placed in the heat-insulating container (temperature during transportation, 4°C to 25°C). The container is sealed with 4 sealing bands for delivery to the manufacturer. The manufacturer should receive the skin tissue within 62 hours after the heat-insulating container has been shipped to the medical institution [see “1. Grafting plan”].

Note: Presumably, each medical institution will follow its own procedure for handling harvested skin tissue and JACE (e.g., special procedures, responsible department). Therefore, the distributor will undertake the

transportation of harvested skin tissue and JACE under the supervision of the manufacturer until a reliable system is established and maintained for the delivery and acceptance of harvested skin tissue and JACE. Once such a system is fully in place, part of the transportation process will be outsourced to a logistics company while the distributor will still be responsible for the rest of the process.

Steps from release at the manufacturer through acceptance at the medical institution

5. Acceptance inspection and handling of the product at the medical institution

(1) A package of cultured epidermis is shipped in a heat-insulating container sealed with bands. The medical institution must ensure that the container is kept sealed before use.

The heat-insulating container is unpacked by cutting the sealing bands with scissors to take out the package of cultured epidermis.

(2) The tissue code (5-digit alphanumeric code) incorporated in the batch number on the package is checked against the order form retained at the medical institution (issued in the step as described in "1. Grafting plan"). The number of the cultured epidermal cell sheets is checked.

(3) The package of cultured epidermis is stored at 10°C to 25°C until immediately before use.

Grafting

6. Procedures before grafting of the cultured epidermal cell sheet

(1) Severe burns

Dermal reconstruction is performed on the site to be treated with the cultured epidermal cell sheet.

(2) Giant congenital melanocytic nevi

The lesion (nevus) is excised. The surgical technique for excision is determined according to the patient's age and nevus size. Dermal reconstruction is performed as necessary.

(3) Dystrophic epidermolysis bullosa and junctional epidermolysis bullosa

The patient's intractable or recurrent erosion/ulcer is treated appropriately with debridement, saline irrigation, etc., as necessary.

7. Grafting of the cultured epidermal cell sheet

(1) Severe burns

The cultured epidermal cell sheet is applied onto the reconstructed dermis. However, the grafting should be preceded by appropriate wound bed preparation such as the removal of necrotic tissue or other factors that render the recipient wound bed unsuitable for grafting, if any.

The cultured epidermal cell sheet may be used on a deep dermal burn wound only when full-thickness and deep dermal burns coexist and it is difficult to treat them separately.

(2) Giant congenital melanocytic nevi

The cultured epidermal cell sheet is applied onto the preserved dermis or reconstructed dermis of a wound after nevus excision.

(3) Dystrophic epidermolysis bullosa and junctional epidermolysis bullosa

The cultured epidermal cell sheet is applied onto the appropriately pre-treated intractable or recurrent erosion/ulcer.

8. The maximum number of cultured epidermal cell sheets to be grafted in a single procedure
Up to 50 pieces of cultured epidermal cell sheets are allowed to be grafted in a single procedure~~, and a total of up to 200 cell sheets in serial procedures~~. ~~The number of cultured epidermal cell sheets used should not exceed these upper limits.~~

(Underline denotes additions/changes and strikethrough denotes deletions.)

Conditions of Approval

1. Because the clinical studies were conducted in extremely limited number of subjects, the applicant is required to conduct a use-results survey covering all patients treated with the product. As a rule, the survey should be continued until the end of the re-examination period. New efficacy and safety data on the product should be communicated appropriately to surgeons/physicians and medical institutions providing treatment with the product, and patient information materials should be updated with the data accordingly.
2. Due to the risks associated with xenotransplantation of 3T3-J2 cells derived from mouse embryo, which are used as feeder cells in the manufacture of the product, the applicant is required to take necessary measures to ensure appropriate handling, such as 30-year retention of a sample of the finished product and a record of use.

Attachment

Review Report (1)

September 7, 2018

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand name	JACE
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Date of application	March 20, 2018

Shape, Structure, Active Ingredient, Quantities, or Definition

An epidermal cell sheet supplied in the package for cultured epidermis is "autologous cultured epidermis" produced from keratinocytes isolated from a patient's own skin tissue. The isolated keratinocytes are cultured into cell sheets for autografting. Cultured (autologous) epidermal cell sheets are grafted onto the wound surface with preserved dermis for the closure of the wound via engraftment/epithelialization. Each container for cultured epidermis contains 1 piece of cultured epidermal cell sheet. A tissue transport tube is used to store and transport the harvested tissue.

Proposed Indication or Performance

1. Severe burns

JACE is indicated for use in patients with serious, extensive burns when sufficient donor sites for autologous skin grafts are not available and the total area of deep dermal and full-thickness burns is 30% or more of the total body surface area. A cultured epidermal cell sheet is applied onto the reconstructed dermis in a full-thickness burn wound to facilitate the closure of the wound. Dermis should be reconstructed with allografts, as a general rule. JACE should be used for deep dermal burn wounds only when full-thickness and deep dermal burns coexist and it is difficult to treat them separately.

2. Giant congenital melanocytic nevi

The cultured epidermal cell sheet is applied onto a wound after excision of giant congenital melanocytic nevi to facilitate the closure of the wound.

3. Dystrophic epidermolysis bullosa and junctional epidermolysis bullosa

JACE is indicated for the treatment of intractable erosions or ulcers in patients with dystrophic or junctional epidermolysis bullosa. The cultured epidermal cell sheet is applied onto an intractable erosion/ulcer to promote epithelialization.

(Underline denotes additions.)

Proposed Dosage and Administration or Method of Use

Grafting plan

1. Grafting plan

A treating surgeon/physician develops a grafting plan and provides the manufacturer of JACE with the details of the plan, which consist of the number of cultured epidermal cell sheets required, the dates of tissue harvest and grafting, the number of grafting procedures, and other necessary information such as on the medical institution and the patient (hereinafter collectively referred to as the "grafting planning information"). The manufacturer prepares an order form indicating a tissue code unique to each grafting plan and the grafting planning information, then send it to the treating surgeon/physician.

The treating surgeon/physician confirms the grafting planning information entered in the order form sent by the manufacturer, before placing an order for production of JACE.

The manufacturer supplies the surgeon/physician with a tissue transport kit (comprising tissue transport tubes) and a dedicated heat-insulating container in time for the date of tissue harvest. The tissue code is indicated on the carton of the tissue transport kit, tissue transport tubes, and heat-insulating container for tissue transportation provided by the manufacturer.

Tissue code

Tissue codes are issued for each grafting plan.

For a patient undergoing tissue harvest more than once, each piece of tissue harvested is identified by a unique tissue code. A grafting plan is developed on a tissue-code basis.

For a patient undergoing a single tissue harvest followed by serial grafting procedures, cultured epidermal cell sheets for multiple grafting procedures are produced using cells derived from the same skin tissue. The tissue code remains unchanged for production of such sheets. Therefore, these sheets are identified with the same tissue code and different batch numbers.

Steps from tissue harvest at the medical institution through the receipt of harvested tissue

2. Tissue harvest

Skin tissue is harvested based on the size of the graft recipient site and according to the grafting plan. The harvested skin should be at least 1 cm^2 in size and elliptical in shape or in such a shape that allows for easier suture. Skin tissue is taken from lesion-free normal skin at any anatomical site. The full-thickness of dermis should be harvested from the donor site.

3. Storage of harvested tissue

The sealing band on the heat-insulating container is cut with scissors to remove the lid and take out the tissue transport kit. The tissue code indicated on the heat-insulating container, carton of the tissue transport kit, and tissue transport tubes is checked against the order form.

The tissue transport kit is unsealed in a clean environment (e.g., operating room, procedure room) to take out the transport tube. The tube is checked for leakage and turbidity of the medium filled in it. If the medium is turbid, the spare tube is used.

The tissue transport tube should not be tilted or shaken unnecessarily.

The tissue transport tube is uncapped. The skin tissue, harvested in a clean environment, is placed in the tube using sterile forceps, etc. to be immersed in the medium. The tube is then capped tightly to prevent a leak of the medium. The date of tissue harvest and the name of the person who performed harvest are indicated on the tube.

4. Transportation of harvested tissue

The tissue transport tube is placed in the carton. The carton is sealed for tamper resistance and placed in the heat-insulating container (temperature during transportation, 4°C to 25°C). The container is sealed with 4 sealing bands for delivery to the manufacturer. The manufacturer should receive the skin tissue within 62 hours after the heat-insulating container has been shipped to the medical institution [see “1. Grafting plan”].

Note: Presumably, each medical institution will follow its own procedure for handling harvested skin tissue and JACE (e.g., special procedures, responsible department). Therefore, the distributor will undertake the transportation of harvested skin tissue and JACE under the supervision of the manufacturer until a reliable system is established and maintained for the delivery and acceptance of harvested skin tissue and JACE. Once such a system is fully in place, part of the transportation process will be outsourced to a logistics company while the distributor will still be responsible for the rest of the process.

Steps from release at the manufacturer through acceptance at the medical institution

5. Acceptance inspection and handling of the product at the medical institution

(1) A package of cultured epidermis is shipped in a heat-insulating container sealed with bands. The medical institution must ensure that the container is kept sealed before use.

The heat-insulating container is unpacked by cutting the sealing bands with scissors to take out the package of cultured epidermis.

(2) The tissue code (5-digit alphanumeric code) incorporated in the batch number on the package is checked against the order form retained at the medical institution (issued in the step as described in “1. Grafting plan”). The number of the cultured epidermal cell sheets is checked.

(3) The package of cultured epidermis is stored at 10°C to 25°C until immediately before use.

Grafting

6. Procedures before grafting of the cultured epidermal cell sheet

(1) Severe burns

Dermal reconstruction is performed on the site to be treated with the cultured epidermal cell sheet.

(2) Giant congenital melanocytic nevi

The lesion (nevus) is excised. The surgical technique for excision is determined according to the patient's age and nevus size. Dermal reconstruction is performed as necessary.

(3) Dystrophic epidermolysis bullosa and junctional epidermolysis bullosa

The patient's intractable erosion/ulcer is treated appropriately with debridement, saline irrigation, etc., as necessary.

7. Grafting of the cultured epidermal cell sheet

(1) Severe burns

The cultured epidermal cell sheet is applied onto the reconstructed dermis. However, the grafting should be preceded by appropriate wound bed preparation such as the removal of necrotic tissue or other factors that render the recipient wound bed unsuitable for grafting, if any.

The cultured epidermal cell sheet may be used on a deep dermal burn wound only when full-thickness and deep dermal burns coexist and it is difficult to treat them separately.

(2) Giant congenital melanocytic nevi

The cultured epidermal cell sheet is applied onto the preserved dermis or reconstructed dermis of a wound after nevus excision.

(3) Dystrophic epidermolysis bullosa and junctional epidermolysis bullosa

The cultured epidermal cell sheet is applied onto the intractable erosion/ulcer that has been treated appropriately with debridement, irrigation, etc., as necessary.

8. The number of sheets to be grafted in a single procedure or serial procedures

Up to 50 pieces of cultured epidermal cell sheets are allowed to be grafted in a single procedure, and a total of up to 200 cell sheets in serial procedures. The number of cultured epidermal cell sheets used should not exceed these upper limits.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

JACE is a combination product. Its primary constituent is a human (autologous) epidermal cell sheet that is produced using the Green's technique. For production of the cultured autologous epidermal cell sheet, keratinocytes are isolated from a postage-stamp sized piece of a patient's own skin tissue and are co-cultured with mouse embryo-derived 3T3-J2 cells as a feeder. The cultured keratinocytes are grown into a sheet. The secondary constituent of the product is a tube (filled with tissue transport medium) used to transport skin tissue harvested from the patient to the manufacturer of JACE.

JACE is a regenerative medical product to be applied onto an erosion or ulcer in patients with epidermolysis bullosa (EB) for the closure and early epithelialization of the wound as with medical devices such as wound dressings.

In Japan, JACE was approved for the indication of severe burns in October 2007 and then for an additional indication of giant congenital melanocytic nevi in September 2016. The product was designated as an orphan medical device as of March 18, 2011 (Orphan Device Designation No. 22 of 2011 [*23 ki*]), with the following intended use or indication: "JACE is indicated for the treatment of intractable erosions/ulcers in patients with epidermolysis bullosa. JACE is applied onto an intractable erosion/ulcer for early epithelialization."

1.2 Development history etc.

EB is a hereditary disease caused by mutations in the genes encoding the structural proteins of the basement membrane and is characterized by inherently fragile skin. The onset of EB is shortly after birth, with a generalized distribution of blisters, erosions, or ulcers occurring at the slightest touch. EB can be divided into 3 major types, depending on the level of blister cleavage, which is different according to types of proteins involved: EB simplex (intraepidermal blistering), junctional EB (blisters within the lamina lucida of the basement membrane zone), and dystrophic EB (subepidermal blistering) (*Textbook of Modern Dermatology*. 3rd ed. Nakayamashoten; 2018:237-8). According to the 1995 survey conducted by the Study Group on Specified Intractable Diseases (rare/intractable skin diseases) that was involved in research programs for intractable diseases supported by the Ministry of Health and Welfare (a predecessor of the Ministry of Health, Labour and Welfare), an estimated 500 to 640 individuals had EB in Japan, and EB simplex, junctional EB, the recessive form of dystrophic EB, the dominant form of dystrophic EB, and other types accounted for 32%, 7%, 33%, 21%, and 7% of all EB cases, respectively. In Japan, EB has been designated as an "intractable disease." A total of 315 EB patients were registered as specific medical expenses (those provided to patients with designated intractable diseases) recipient certificate holders in FY 2016 (http://www.nanbyou.or.jp/entry/5354).

There is no curative treatment for a genetic disease, EB, and supportive care is the mainstay of treatment. Supportive measures include waiting for spontaneous wound closure, in addition to providing patients with advice on how to avoid trauma and friction to the skin for the prevention of blistering. Specifically, blister fluid is removed, antibiotic ointments are topically applied on erosions or ulcers for the prevention of infections,

topical therapy is used, gauze or special wound dressings are used for protection. However, many of erosions or ulcers become chronic and resistant to healing, and long-term continuous treatment is therefore inevitable. This leads to clinical problems such as deterioration in nutritional status, persistent pain, infections, syndactyly, and squamous cell carcinoma arising from ulcers.

Recently, published literature reported cases of dystrophic or junctional EB successfully treated with cultured epidermal autografts generated using the Green's technique (cases resulting in epithelialization and healing of the wounds) (*Acta Derm Venereol.* 2014; 94:98-9, *Clin Exp Dermatol.* 2006; 31:718-9). The Green's technique was developed by Howard Green et al. of the Harvard Medical School (the US) in 1975. The cultured epidermal autograft generated using the Green's technique including JACE has not been approved for the indication of EB in any country or region at present. The applicant started the clinical development of JACE, human autologous epidermal cell sheets, to be applied onto intractable erosions/ulcers in patients with dystrophic or junctional EB to promote epithelialization, and recently filed a partial change application for the regenerative medical product.

2. Manufacturing Process and Specifications

Because the present application is intended to expand the indication, data on manufacturing process and specifications have not been submitted.

3. Stability

Because the present application is intended to expand the indication, stability data have not been submitted.

4. Indication or Performance and Outline of the Review Conducted by PMDA

Although the present application is intended to expand the indication, characterization or pharmacology data etc. have not been submitted to support the efficacy or performance of JACE in the treatment of erosions or ulcers in EB patients.

The applicant's explanation about its mechanism of promoting epithelialization of erosions or ulcers in EB patients:

The mechanism of action of the cultured epidermal cell sheet, JACE, is as follows: (1) Keratinocytes of the sheet come in contact with the wound surface due to compression of the graft with a wound dressing etc. or a simple adhesive force of the exudate of the wound. (2) The keratinocytes in contact with the wound surface produce cell adhesion molecules such as cadherin and adhere to the dermal layer. (3) The keratinocytes begin to proliferate while desmosomes are formed between the cells by desmogleins belonging to the cadherin family. Hemidesmosomes are formed between the keratinocytes and the dermal tissue through the interaction of integrin with laminin-332, resulting in the adhesion of the keratinocytes to the dermal layer. (4) The keratinocytes proliferate adhering to the dermal layer until the entire wound is covered. The basement membrane is a complex structure composed of many proteins. Even if some of these proteins are reduced or missing, the proliferation or engraftment of keratinocytes will not be affected significantly, though the adhesive strength may be altered. There should be no differences between EB and the previously approved indication,

severe burns, in terms of the fact that the skin becomes damaged and ulcerates. JACE grafting is presumed to promote the adhesion of keratinocytes to the dermis, leading to early epithelialization also in patients with EB.

4.R Outline of the review conducted by PMDA

PMDA's view:

No characterization or pharmacology studies, etc. have been conducted to obtain evidence supporting the contribution of JACE to epithelialization of erosions or ulcers in EB patients with a mutation in the gene encoding a specific structural protein of the basement membrane. Thus, the mechanism by which JACE produced from an EB patient's skin tissue contributes to epithelialization of erosions or ulcers remains unclarified.

5. Biodistribution of the Product

Because the present application is intended to expand the indication, biodistribution data have not been submitted.

6. Nonclinical Safety Data

Because the present application is intended to expand the indication, nonclinical safety data have not been submitted.

7. Clinical Data and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the results from the following 2 studies: a Japanese phase II study (Study J-TEC-EB) and an investigator-initiated Japanese phase III study (Study J-TEC-01-01). The applicant also submitted the interim data from long-term follow-up clinical research on patients who were treated with JACE in Study J-TEC-01-01 as efficacy and safety reference data.

7.1 Evaluation data

7.1.1 Japanese clinical studies

7.1.1.1 Study J-TEC-EB (Attached document 1; Studied period, [redacted] to [redacted])

An open-label, uncontrolled, Japanese phase II study (a feasibility study) was conducted at 4 sites to investigate the efficacy and safety of JACE in patients with dystrophic EB who had an ulcer of ≥10 cm^2 in size that were likely to last for ≥4 weeks (target sample size, 3 subjects). In this study, "the observation phase" was the period from the date of obtaining consent until the initial grafting of JACE, and "the treatment phase" was the period following the initial grafting of JACE. After ≥4 weeks of observation, subjects were grafted with JACE and followed-up during the treatment phase (12 weeks after the initial grafting).

For tissue harvest, a piece of full-thickness skin of several cm^2 was to be taken from the patient's normal-appearing skin area (skin with no macroscopic abnormalities such as erosions and ulcers) wherever possible. While up to 50 pieces of JACE sheets were allowed to be grafted in a single procedure, there was no limit on the number of ulcers to be grafted with JACE (target ulcers). Eligible patients had to have ulcers that were ≥10 cm^2 in size and of ≥4 weeks' duration at the time of enrollment in the treatment phase or ulcers that were ≥5

cm^2 in size at the time of enrolment in the observation phase and then enlarged to a size of ≥10 cm^2 by the time of enrollment in the treatment phase. However, ulcers that clearly tended to reduce in area were excluded from evaluation. The need for re-grafting with JACE was determined based on the extent of epithelialization at 2 and 6 weeks after the initial grafting. If the percent epithelialization was ≤50% at 4 and 8 weeks after the initial grafting of JACE, re-grafting was to be performed. Only ulcers grafted with JACE in the initial procedure were to be grafted with JACE in an additional grafting procedure, and up to 3 grafting procedures including the initial procedure, were allowed to be performed.

Four patients with recessive dystrophic EB were enrolled in the observation phase of the study (Table 1) and included in the observation-phase safety analysis set. Of these, 1 subject (D-1) was excluded from evaluation because JACE could not be produced due to poor cell proliferation, though the subject had tissue harvested thrice. Other 3 subjects treated with JACE were included in the treatment-phase safety analysis set and in the full analysis set (FAS). One more subject (B-1) was excluded from the FAS because the subject failed to meet the inclusion criteria for the treatment phase of the study.[1)] The remaining 2 subjects were included in the per protocol set (PPS), and the PPS was the primary efficacy analysis set. Table 1 shows the characteristics of individual subjects and specific grafting information. None of the patients were re-grafted.

Table 1. Characteristics of individual subjects and specific grafting information

Subject ID	Inclusion in PPS	Age (years)	Sex	Donor site size (cm^2)	No. of target ulcers	No. of sheets grafted	Time from tissue harvest to JACE grafting (days)	Additional information
A-1	Yes	11	Female	2	1	1	35	—
B-1	No	55	Male	2	5	3	50	Subject failed to meet the inclusion criteria for the treatment phase of the study.[1)]
C-1	Yes	15	Female	2	2	10	43	—
D-1	No	36	Male	2 (first) 2 (second) 3 (third)	—	—	—	JACE could not be produced due to poor cell proliferation for all harvested tissues.

The primary endpoint of the study was the percent epithelialization (%) at 4 weeks after the last grafting for each target ulcer. The percent epithelialization was determined by macroscopically assessing the percentage of the epithelialized area relative to the ulcer area at baseline in 10 percentage point increments. Although the primary analysis of the primary endpoint using a linear mixed-effects model had been planned, estimation was not possible, precluding evaluation based on this analysis. Table 2 shows ulcer size at baseline (at the time of JACE grafting) and the percent epithelialization (%) at 4 weeks after the last grafting for each target ulcer of each subject.

[1)] The subject failed to meet the inclusion criteria because all ulcers were <10 cm^2 at the time of enrollment in the treatment phase. However, treatment with JACE was considered necessary by the investigator, for the following reasons: (1) his individual ulcers were persistent, (2) there was no alternative treatment, and (3) tissue had already been taken from normal-appearing skin for the production of JACE. Eventually, the subject was grafted with JACE.

Table 2. Percent epithelialization at 4 weeks after the last grafting for each subject (%) (FAS)

Subject ID	Target ulcer	Location of ulcer	Ulcer size at baseline (at the time of JACE grafting) (cm^2)	Percent epithelialization at 4 weeks after the last grafting (%)
A-1	A-1-1	Left upper dorsal region	16.3	90
B-1	B-1-1	Anterior left lower leg	3.3	100
	B-1-2	Anterior left lower leg	1.9	100
	B-1-3	Anterior left lower leg	4.1	100
	B-1-4	Anterior left lower leg	6.8	100
	B-1-5	Posterior left lower leg	7.9	100
C-1	C-1-1	Entire right upper arm	107.8	80
	C-1-2	Entire left upper arm	93.0	80

Table 3 shows the percent epithelialization at 1, 2, 3, 4, 6, 8, and 12 weeks after the initial grafting for each target ulcer.

Table 3. Percent epithelialization over time for each target ulcer

Subject ID	Target ulcer	Percent epithelialization after JACE grafting (%)						
		1 week	2 weeks	3 weeks	4 weeks	6 weeks	8 weeks	12 weeks
A-1	A-1-1	70	90	80	90	80	80	80
B-1	B-1-1	50	70	100	100	100	70	30
	B-1-2	60	50	100	100	100	0	100
	B-1-3	60	100	100	100	100	100	40
	B-1-4	60	90	90	100	50	100	40
	B-1-5	40	90	100	100	60	70	100
C-1	C-1-1	80	80	80	80	80	90	90
	C-1-2	80	80	80	80	80	90	90

Safety results for individual subjects are shown below.

1) Subject A-1

An adverse event reported during the observation phase was pain of skin (Grade 1, non-serious, resolved), and its causal relationship to a study procedure (tissue harvest) could not be ruled out. This event occurred at the donor site on the day after tissue harvest. During the treatment phase, skin ulcer (Grade 2, non-serious, unresolved), nasopharyngitis (Grade 2, non-serious, resolved), bacterial infection (Grade 2, non-serious, unresolved), and otitis media (Grade 2, non-serious, resolving) were observed, and all those events were considered unrelated to JACE. The skin ulcer occurred at the donor site, i.e. the left chest, at 34 days after JACE grafting, and its causal relationship to a study procedure (tissue harvest) could not be ruled out. The event was considered to be caused by mechanical stress in daily activities. The bacterial infection occurred at the graft recipient site at 6 days after JACE grafting and was considered to be caused by indigenous bacteria due to long-term coverage after grafting. Its causal relationship to a study procedure could not be ruled out.

2) Subject B-1

No adverse events were reported during the observation phase. During the treatment phase, eczema asteatotic (Grade 2, non-serious, unresolved) and oral herpes (Grade 1, non-serious, resolved) were observed, and both events were considered unrelated to JACE. The eczema asteatotic occurred at the graft recipient site at 43 days after JACE grafting and was considered to be caused by long-term coverage after grafting. Its causal relationship to a study procedure could not be ruled out.

3) Subject C-1

No adverse events were reported during the observation phase. During the treatment phase, pyrexia (Grade 1, non-serious, resolved) and pruritus (Grade 2, non-serious, resolved) were noted, and both events were considered unrelated to study procedures including tissue harvest or JACE.

4) Subject D-1

No adverse events were reported during the observation phase.

7.1.1.2 Study J-TEC-01-01 (Attached document 2; Studied period, [redacted] to [redacted])

An open-label, uncontrolled, investigator-initiated Japanese phase III study (a pivotal study) was conducted at 1 site to evaluate the efficacy and safety of JACE in patients with severe recessive dystrophic or junctional EB in whom a genetic mutation causing EB (a compound heterozygote mutation or a homozygote mutation in genes encoding the alpha 1 chain of type VII collagen [*COL7A1*], the alpha 1 chain of type XVII collagen [*COL17A1*], or laminin-332 [laminin subunit alpha 3 (*LAMA3*), laminin subunit beta 3 (*LAMB3*), laminin subunit gamma 2 (*LAMC2*)]) had been identified by genetic testing (target sample size, ≥3 subjects). In this study, "the observation phase" was the period from the date of obtaining consent until the initial grafting of JACE, and "the treatment phase" was the period from the initial grafting of JACE until the last time point. After ≥4 weeks of observation, subjects were grafted with JACE and followed-up during the treatment phase (24 weeks after the initial grafting).

For tissue harvest, a piece of full-thickness skin of 2 to 5 cm^2 was to be taken from the patient's normal-appearing skin reflecting "revertant mosaicism" (a naturally occurring phenomenon involving spontaneous correction of a pathogenic mutation in a somatic cell), which was identified by an overall evaluation, including gross evaluation by the investigator or sub-investigator and evaluation of resistance to mechanical stress by rub test with ballpoint pen,[2)] adhesive strip test,[3)] and mechanical rubber stress test.[4)] Up to 50 pieces of JACE were allowed to be grafted in a single procedure, and there was no limit on the number of target ulcers. The investigator or sub-investigator determined the eligibility of each ulcer (intractable or recurrent ulcer) for grafting with JACE in the study. Intractable ulcers were defined as ulcers of ≥4 weeks' duration, and recurrent ulcers were defined as ulcers characterized by repeated cycles of ulceration and re-epithelialization during the observation phase (ulcers that had healed by scarring by the first day of observation phase, recurred during the observation phase, and were still present on the first day of treatment phase, or ulcers that had formed by the first day of observation phase, were epithelialized temporarily [from patient interview] during the observation phase, and recurred by the first day of treatment phase). Although the size or location of ulcers was not specified, ulcers deemed inappropriate for grafting by the investigator or sub-investigator (e.g., ulcers with evident infections) were excluded. The need for re-grafting with JACE was determined at 2 and 6 weeks after the initial

[2)] With a quick movement, the tip of a retracted ballpoint pen is pushed over the skin for a distance of 2 to 4 mm, for skin fragility assessment (*J Invest Dermatol*. 2014; 134: 2097-104).

[3)] Fixomull Stretch 1 cm×2 cm (an adhesive tape) is placed on the skin area and pulled off by a strong force to check if the skin detaches, for skin fragility assessment (*J Invest Dermatol*. 2014; 134: 2097-104).

[4)] The skin is gently stretched, and mechanical shearing forces are applied by repeated (25 times) rubbing with a pencil eraser to check if an ulcer forms, for skin fragility assessment (*J Am Acad Dermatol*. 2012; 67: 904-17, *J Clin Invest*. 2008; 118: 1669-79).

grafting. If the percent epithelialization of the target ulcer at 4 and 8 weeks after the initial grafting of JACE was <50% as determined by the investigator or sub-investigator based on the photograph of the graft recipient site, re-grafting was to be performed. The percent epithelialization was calculated using image processing software, Image J. Only ulcers grafted with JACE in the initial procedure were to be grafted with JACE in an additional grafting procedure, and up to 3 grafting procedures, including the initial procedure, were allowed to be performed.

Three patients with recessive dystrophic EB were enrolled in the study. The 3 subjects treated with JACE were included in the safety analysis set and in the FAS, and the FAS was used for efficacy analyses. Table 4 shows the characteristics of individual subjects and specific grafting information. Subject H-01 was re-grafted at 4 and 8 weeks after the initial grafting, and Subject H-02 or H-03 was not re-grafted.

Table 4. Characteristics of individual subjects and specific grafting information

Subject ID	Age (years)	Sex	Donor site size (cm^2)	No. of target ulcers	No. of sheets grafted	Time from tissue harvest to initial grafting (days)	Additional information
H-01	26	Male	4	4	4 (initial grafting) 3 (re-grafting at 4 weeks after the initial grafting) 4 (re-grafting at 8 weeks after the initial grafting)	30	—
H-02	48	Female	5 (first) 5 (second)	1	1	107	JACE could not be produced with the first tissue harvested, and production was successful with the second tissue harvested.
H-03	61	Female	5	3	3	28	—

The primary endpoint of the study was the percent epithelialization (%) at 4 weeks after the last grafting for each subject,[5)] which was determined based on the ulcer size calculated from the photograph of the graft recipient site using image processing software, Image J, by the independent central review committee.

The percent epithelialization at 4 weeks after the last grafting was 57.01% for Subject H-01, 100.00% for Subject H-02, and 87.70% for Subject H-03. The mean percent epithelialization at 4 weeks after the last grafting with its 95% confidence interval was 81.57% (26.57%, 100.00%), and the lower limit of the 95% confidence interval exceeded the pre-specified threshold (1%).

Table 5 shows ulcer size at baseline (at the time of the initial grafting) and the percent epithelialization at 4 weeks after the last grafting for each target ulcer.

[5)] The change in the area of each target ulcer (ulcer size at the time of the initial grafting − ulcer size at 4 weeks after the last grafting) was calculated, and the sum of changes in the area of all ulcers was divided by the sum of the areas of all ulcers at the time of the initial grafting.

Table 5. Percent epithelialization at 4 weeks after the last grafting for each target ulcer (central review) (FAS)

Subject ID	Target ulcer	Location of ulcer	Ulcer type	Ulcer size at baseline (at the time of initial grafting) (cm^2)	Percent epithelialization at 4 weeks after the last grafting (%)
H-01	H-01-1	Posterior neck	Intractable	14.3	55.94
	H-01-2	Left upper dorsal region	Intractable	35.5	36.90
	H-01-3	Right upper dorsal region	Intractable	12.3	59.35
	H-01-4	Posterior left axilla	Intractable	24.9	85.14
H-02	H-02-1	Right chest	Recurrent	2.0	100.00
H-03	H-03-1	Around right supraclavicular fossa	Recurrent	2.5	88.00
	H-03-2	Left chest	Recurrent	6.6	69.70
	H-03-3	Posterior right thigh	Recurrent	9.6	100.00

Table 6 shows the percent epithelialization at 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 weeks after the initial grafting for each target ulcer.

Table 6. Percent epithelialization (central review) over time for each target ulcer

Subject ID	Target ulcer	Percent epithelialization after JACE grafting (%)									
		1 week	2 weeks	3 weeks	4 weeks	6 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks
H-01	H-01-1	38.46	73.43	37.76	53.15*	60.14	39.86*	55.94	53.85	38.46	79.72
	H-01-2	23.94	49.58	32.68	58.31	61.41	28.45*	36.90	43.94	29.30	3.94
	H-01-3	73.17	95.93	0.00	0.00*	0.00	12.20*	59.35	0.00	62.60	44.72
	H-01-4	51.81	89.96	78.31	29.72*	97.59	53.82*	85.14	85.94	95.18	81.12
H-02	H-02-1	90.00	100.00	100.00	100.00	100.00	100.00	100.00	0.00	100.00	90.00
H-03	H-03-1	88.00	88.00	44.00	88.00	72.00	68.00	100.00	80.00	80.00	76.00
	H-03-2	90.91	96.97	95.45	69.70	100.00	89.39	96.97	98.48	96.97	93.94
	H-03-3	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

*Since the percent epithelialization as determined by the investigator or sub-investigator was <50%, re-grafting was performed.

Safety results for individual subjects are shown below.

1) Subject H-01

No adverse events were reported during the observation phase. During the treatment phase, musculoskeletal stiffness (Grade 1, non-serious, unresolved) was observed, and the event was considered unrelated to study procedures including tissue harvest or JACE.

2) Subject H-02

Adverse events observed during the observation phase were squamous cell carcinoma (Grade 3, serious, resolving), wound dehiscence (Grade 2, non-serious, resolved), blepharitis (Grade 2, non-serious, unresolved), procedural pain (Grade 2, non-serious, resolved), nausea (Grade 2, non-serious, resolved), nephrogenic anaemia (Grade 3, non-serious, resolved), and staphylococcal infection (Grade 2, non-serious, resolved). These events, except wound dehiscence, were considered unrelated to study procedures including tissue harvest. A causal relationship of the wound dehiscence to a study procedure (tissue harvest) could not be ruled out because the subject had the wound dehiscence at the donor site. During the treatment phase, squamous cell carcinoma (Grade 3, serious, resolving), transfusion reaction (Grade 2, non-serious, resolved), procedural pain (Grade 2, non-serious, resolved), otitis externa (Grade 2, non-serious, unresolved), diarrhoea (Grade 1, non-serious, resolved), nausea (Grade 2, non-serious, resolved), and nephrogenic anaemia (Grade 3, non-serious, resolved)

were observed. The events were considered unrelated to study procedures including tissue harvest or JACE. Squamous cell carcinoma is an expected adverse event in light of the characteristics of the primary disease. This event was a condition existing before JACE grafting and considered unrelated to JACE.

3) Subject H-03

No adverse events were reported during the observation phase. During the treatment phase, cellulitis (Grade 2, non-serious, resolved), osteoarthritis (Grade 1, non-serious, unresolved), and synovitis (Grade 1, non-serious, unresolved) were observed, and a causal relationship to study procedures including tissue harvest and JACE was denied for all those events.

7.2 Reference data

7.2.1 Japanese clinical research (Research period, [redacted] ([redacted], [redacted], [redacted], [redacted]))

Clinical research was conducted to follow up patients who were treated with JACE in Study J-TEC-01-01 (a prospective observational study). The clinical research was intended to evaluate the long-term efficacy and safety of JACE in patients with EB. Subjects H-01, H-02, and H-03 gave their consent on the day of completing the follow-up period of Study J-TEC-01-01 and entered this study.

Table 7 shows the percent epithelialization for each target ulcer, which was determined based on the photograph of the site that was grafted with JACE in Study J-TEC-01-01, using image processing software, Image J.

Table 7. Percent epithelialization over time
from the end of follow-up period of Study J-TEC-01-01 (24 weeks after the initial grafting)

Subject ID	Target ulcer	Percent epithelialization (%)			
		3 months	6 months	9 months	12 months
H-01	H-01-1	37.1	67.1	46.2	44.1
	H-01-2	34.4	33.5	22.5	18.9
	H-01-3	37.4	37.4	51.2	66.7
	H-01-4	51.0	77.1	26.9	98.8
H-02	H-02-1	100.0	100.0	100.0	80.0
H-03	H-03-1	75.5	67.3	71.4	100.0
	H-03-2	100.0	100.0	100.0	100.0
	H-03-3	100.0	100.0	100.0	100.0

Safety data were evaluated. As of [redacted], no adverse events for which a causal relationship to the procedures of Study J-TEC-01-01 or JACE cannot be ruled out have occurred at the sites that were grafted with JACE in Study J-TEC-01-01. The following adverse events occurred at the sites that were not grafted with JACE in Study J-TEC-01-01. Squamous cell carcinoma on the dorsum of right foot was excised in Subject H-01. Subject H-02 was treated as an inpatient at the internal medicine department because retention of pleural effusion in the right lung was noted. In addition, squamous cell carcinoma developed on the right foot of Subject H-02 and was excised. Then squamous cell carcinoma recurred at the same site and was excised again. Subject H-03 underwent left mastectomy because left breast cancer was noted. The subject also had a diagnosis of pyogenic osteomyelitis of the left index finger and treated as an inpatient. All of these adverse events

occurred at the sites other than the graft recipient sites. The events were considered unrelated to the procedures of Study J-TEC-01-01 and JACE.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

The applicant's explanation about the rationale for the primary endpoint (the percent epithelialization at 4 weeks after the last grafting) for Studies J-TEC-EB and J-TEC-01-01 and the efficacy of JACE in EB patients:
The objective of JACE grafting in EB patients is to promote the epithelialization of ulcers. If epithelialization proceeds smoothly, the basement membrane structure will be restored at 4 weeks after JACE grafting. Therefore, the result at 4 weeks after JACE grafting was considered to best reflect the therapeutic effect of JACE. In addition, re-grafting might be necessary for some of the graft recipient sites. For these reasons, the percent epithelialization at 4 weeks after the last grafting during the study period was selected as the primary endpoint. Further, a report on a consensus approach to wound care in EB reads that a wound size reduction of 20% to 40% at 2 and 4 weeks after treatment is a reliable predictor of healing at 12 weeks after treatment (*J Am Acad Dermatol.* 2012; 67: 904-17). Given this, the expected percent epithelialization of the wound treated with JACE at 4 weeks after the last grafting was assumed to be 50% in Study J-TEC-01-01.

In Study J-TEC-EB that was intended to investigate the efficacy and safety of JACE in patients with dystrophic EB (a feasibility study), all of 8 target ulcers achieved ≥80% epithelialization at 4 weeks after the last grafting. In Study J-TEC-01-01 that was intended to evaluate the efficacy and safety of JACE produced from areas of revertant mosaicism in patients with recessive dystrophic or junctional EB, the mean percent epithelialization at 4 weeks after the last grafting in the FAS (3 patients with recessive dystrophic EB) was 81.57% (95% CI, 26.57%, 100.00%), and the lower limit of the 95% confidence interval exceeded the pre-specified threshold (1%). The results of these 2 studies demonstrated the efficacy of JACE in patients with dystrophic EB.

Follow-up clinical research on patients who were treated with JACE in Study J-TEC-01-01 showed that almost complete epithelialization was maintained in Subjects H-02 and H-03 while the percent epithelialization varied over time in Subject H-01.

PMDA's view:
Only 6 subjects were treated with JACE in Study J-TEC-EB or J-TEC-01-01. This poses limitations to the evaluation of study results. Meanwhile, JACE grafted onto intractable or recurrent ulcers in patients with dystrophic EB showed a certain degree of epithelialization, and the recipient site remained epithelialized 1 year after the end of follow-up period of Study J-TEC-01-01. Thus, these studies demonstrated a certain level of efficacy of JACE in patients with dystrophic EB. However, re-grafting was needed for an ulcer due to inadequate epithelialization after the initial grafting of JACE. The applicant should collect post-marketing information on the percent epithelialization after re-grafting with JACE.

Since the currently available information on the efficacy of JACE is very limited, the applicant should collect post-marketing information on the efficacy of JACE.

Study J-TEC-01-01 could not enroll patients with junctional EB who were also the intended patient population. Thus, no study data on this patient population are available. The efficacy of JACE in patients with junctional EB is discussed in Section 7.R.3.

7.R.2 Safety

PMDA reviewed adverse events observed in Studies J-TEC-EB and J-TEC-01-01. There are no major differences in the safety profile of JACE between EB and the previously approved indications. No new clinically relevant adverse events of special interest occurred in patients with EB. However, 1 subject had skin ulcer (unresolved) at the donor site in Study J-TEC-EB. Given the pathology of EB, ulcers are likely to occur at the donor site and may be persistent as compared to the previously approved indications. Thus, the clinical course after tissue harvest should be watched for.

7.R.3 Clinical positioning and indication or performance

The proposed indication or performance for JACE is "dystrophic epidermolysis bullosa and junctional epidermolysis bullosa; JACE is indicated for the treatment of intractable erosions or ulcers in patients with dystrophic or junctional EB. The cultured epidermal cell sheet is applied onto an intractable erosion/ulcer to promote epithelialization."

The applicant's explanation about the clinical positioning of JACE in the treatment of EB:
Patients with dystrophic or junctional EB typically have intractable erosions or ulcers. Although the level of cleavage at the dermal-epidermal junction differs by the subtypes due to different proteins affected, the mechanism of the disease is similar between dystrophic and junctional EB. While the severity of the disease differs from patient to patient, the main clinical symptoms are intractable erosions and ulcers, pain, etc., in both types of EB. Because persistent ulcers and re-ulceration pose clinical problems, early epithelialization of the wounds is needed for both dystrophic and junctional EB.

In Studies J-TEC-EB and J-TEC-01-01, a high percentage of epithelialization was observed after JACE grafting in patients with dystrophic EB. Although no patients with junctional EB were enrolled in the studies, cases of junctional EB successfully treated with cultured epidermal autografts generated using the Green's technique, which are similar to JACE (resulting in epithelialization and healing of the wounds), have been reported overseas. Given these findings, JACE will offer a treatment option for patients with dystrophic or junctional EB (*Clin Exp Dermatol*. 2006; 31: 718-9).

PMDA's view:
The target disease, EB, is a hereditary disease caused by mutations in the genes encoding the structural proteins of the basement membrane. There is no curative treatment, and the currently available treatments are limited to supportive measures, such as antibiotic ointments for the prevention of infections, topical therapy, and wound dressings for protection.

As described in Section "7.R.1 Efficacy," the submitted study data demonstrated a certain level of efficacy of JACE in patients with dystrophic EB. On the other hand, no clinical study data on the efficacy of JACE in patients with junctional EB have been obtained, and the impact of differences in structural protein gene mutations between the different types of EB on the efficacy of JACE remains unclear. However, given that patients with dystrophic EB treated with JACE achieved a certain degree of epithelialization in Studies J-TEC-EB and J-TEC01-01 and that published literature reported cases of junctional EB successfully treated with cultured epidermal autografts generated using the Green's technique, which are similar to JACE (resulting in epithelialization and healing of the wounds) (*Clin Exp Dermatol*. 2006; 31: 718-9), JACE produced from autologous skin tissue that is considered normal-appearing skin can be effective also in patients with junctional EB. Junctional EB is a very rare disease, accounting for 7% of all cases of EB. It is understandable that a clinical study involving patients with junctional EB is infeasible. Thus, the applicant should collect and review post-marketing information on the safety and efficacy of JACE in patients with junctional EB.

Based on the above, the proposed indication or performance of "dystrophic epidermolysis bullosa and junctional epidermolysis bullosa" is appropriate. However, the indication statement ("JACE is indicated for the treatment of intractable erosions or ulcers in patients with dystrophic or junctional epidermolysis bullosa. The cultured epidermal cell sheet is applied onto an intractable erosion/ulcer to promote epithelialization.") should be amended to "JACE is indicated for the treatment of intractable or recurrent erosions/ulcers in patients with dystrophic or junctional epidermolysis bullosa. The cultured epidermal cell sheet is applied onto an intractable or recurrent erosion/ulcer to promote epithelialization." so that the indication includes the use of JACE for the treatment of recurrent ulcers (ulcers characterized by repeated cycles of ulceration and re-epithelialization), which was studied in Study J-TEC-01-01. Taking account of the criteria for determining if ulcers should be grafted with JACE during the observation phase in Studies J-TEC-EB and J-TEC-01-01, the definition of "intractable or recurrent erosions or ulcers" should be stated in the "Precautions for Indication or Performance " section of the package insert, and the statement should be as follows: "JACE should be used to treat an erosion or ulcer of approximately 4 weeks' duration or an erosion or ulcer characterized by repeated cycles of ulceration and re-epithelialization."

The indication or performance for JACE will be finalized, taking account of comments from the Expert Discussion.

7.R.4 Dosage and administration or method of use

7.R.4.1 Tissue harvest

The applicant's explanation about tissue harvest for the production of JACE:

In Study J-TEC-EB, a piece of full-thickness skin was taken from the patient's normal-appearing skin area (skin with no macroscopic abnormalities such as erosions and ulcers) wherever possible. In Study J-TEC-01-01, a piece of full-thickness skin was taken from the patient's normal-appearing skin reflecting revertant mosaicism, which was identified by an overall evaluation, including gross evaluation by the investigator or

sub-investigator and evaluation of resistance to mechanical stress by rub test with ballpoint pen,[6] adhesive strip test,[7] and mechanical rubber stress test.[8]

Although the rule for tissue harvest was different between the 2 studies, high percent epithelialization was observed in the both studies. For this reason, the efficacy of JACE can be promising even when JACE is produced from skin tissue taken from just macroscopically normal-appearing skin areas.

The following information will be provided for post-marketing clinical use: If the patient has multiple macroscopically normal-appearing skin areas, resistance to mechanical stress should also be evaluated by rub test with ballpoint pen,[6] which is considered feasible and most common in clinical practice, to select the donor site.

PMDA's view:
Although the rule for tissue harvest was different between Studies J-TEC-EB and J-TEC-01-01, high percent epithelialization was observed after JACE grafting in the both studies. Thus, the efficacy of JACE can be promising even when JACE is produced from skin tissue taken from just macroscopically normal-appearing skin areas. The applicant's explanation (if the patient has multiple macroscopically normal-appearing skin areas, the donor site will be selected, also referring to the results of evaluation of resistance to mechanical stress.) is understandable. Thus, as long as information on tissue harvest for the production of JACE is provided appropriately, the addition of specific conditions is not necessary in the "Dosage and Administration or Method of Use" section of the package insert.

7.R.4.2 Treatment before JACE grafting

The applicant's explanation about treatment before JACE grafting:
In Study J-TEC-01-01, the wounds were treated appropriately with debridement, saline irrigation, etc., as necessary, at the discretion of the investigator, before JACE grafting. Thus, this procedure will be described also in the "Dosage and Administration or Method of Use" section of the package insert.

PMDA accepted the applicant's explanation.

The dosage and administration or method of use for JACE will be finalized, taking account of comments from the Expert Discussion.

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[6] With a quick movement, the tip of a retracted ballpoint pen is pushed over the skin for a distance of 2 to 4 mm, for skin fragility assessment (*J Invest Dermatol*. 2014; 134: 2097-104).
[7] Fixomull Stretch 1 cm×2 cm (an adhesive tape) is placed on the skin area and pulled off by a strong force to check if the skin detaches, for skin fragility assessment (*J Invest Dermatol.* 2014; 134: 2097-104).
[8] The skin is gently stretched, and mechanical shearing forces are applied by repeated (25 times) rubbing with a pencil eraser to check if an ulcer forms, for skin fragility assessment (*J Am Acad Dermatol*. 2012; 67: 904-17, *J Clin Invest*. 2008; 118: 1669-79).

7.R.5 Success or failure of JACE production

The applicant's explanation about the cases of failure of JACE production in Studies J-TEC-EB and J-TEC-01-01:

In Study J-TEC-EB, tissue was harvested thrice, but JACE could not be produced for 1 subject (D-1). In Study J-TEC-01-01, JACE could not be produced with the first tissue harvested and JACE production was successful with the second tissue harvested for 1 subject (H-02). Although the definitive cause of production failure was unknown, both patients had deterioration of general condition (e.g., chronic renal failure or anemia). Not only the condition of the donor site but also the management of general conditions would be important for tissue harvest. In the post-marketing setting, it is desirable to ensure that patients have good general conditions, before harvesting tissue.

PMDA's view:

There are limitations to evaluation due to limited experience of producing JACE using skin tissue harvested from EB patients. Since multiple cases of failure of JACE production were reported in 2 clinical studies involving a total of 6 EB patients, the pathology of EB may affect the success or failure of JACE production. The applicant should conduct a post-marketing survey to investigate the cause of failure of JACE production after tissue harvest and thereby collect information on the success or failure of JACE production. If information on appropriate tissue harvest for the production of JACE becomes available, such information should be communicated to healthcare professionals in clinical practice in an appropriate and prompt manner.

7.R.6 Qualifications of medical institutions and surgeons/physicians for using JACE

EB is a rare disease, and this indicates the limited availability of surgeons/physicians with experience in treating EB. PMDA asked the applicant to explain the requirements for medical institutions and surgeons/physicians to handle JACE properly in the post-marketing setting.

The applicant's explanation:

Before JACE grafting, EB patient's intractable erosion or ulcer needs to be treated appropriately with debridement, saline irrigation, etc., as necessary. For the proper use of JACE in the post-marketing setting, medical institutions are required to have facilities and staff necessary to provide postoperative management. JACE should be appropriately handled by specialists with adequate knowledge, skills, and experience in treatment of EB; specifically, dermatologists, plastic surgeons, or pediatricians. After marketing, the applicant will provide information and training for the proper use of JACE to surgeons/physicians with no relevant experience.

PMDA's view:

Given that JACE is used by the specialist doctors and at medical institutions meeting the above-mentioned requirements, the specialist doctors should be informed and trained through written materials etc., which describe the nature of JACE, grafting procedure, treatment before and after grafting, precautions for use, etc.

The qualifications of surgeons/physicians and medical institutions and other necessary information to be communicated to them for the proper use of JACE will be finalized, taking account of comments from the Expert Discussion.

8. Risk Analysis and Outline of the Review Conducted by PMDA

The applicant's explanation about post-marketing use-results survey plan for JACE:

A post-marketing use-results survey is planned to be conducted in EB patients treated with JACE to assess the safety, etc. of JACE in routine clinical practice. The survey is intended to include all patients who undergo tissue harvest for the production of JACE during the re-examination period. The observation period will begin at the time of tissue harvest for the production of JACE and end at 16 weeks after the initial grafting. This period was selected assuming that the skin has undergone 2 cycles of turnover (the process of skin turnover takes approximately 6 weeks) after graft take (at presumably 4 weeks after grafting) (*Textbook of Modern Dermatology*. 3rd ed. Nakayamashote; 2018:3). The observation is intended to assess epithelialization after JACE grafting and stability after epithelialization, taking account of the risk of re-ulceration in EB. Safety can also be assessed appropriately by collecting safety information up to 16 weeks after the initial grafting.

Survey items are patient characteristics (including type of EB, ulcer size and the presence or absence of infections at the graft recipient site, information on tissue harvest [e.g., anatomic site, donor site size, description]), safety (adverse events, clinically significant adverse reactions (the events possibly related to JACE grafting [neoplastic lesions at the graft recipient site, allergic symptoms, unknown infections of unknown cause]), and malfunctions), efficacy (percent epithelialization and objective symptoms [blisters/ulcers]), and information on the success or failure of JACE production. Key survey items are clinically significant adverse reactions (the events possibly related to JACE grafting [neoplastic lesions at the graft recipient site, allergic symptoms, unknown infections of unknown cause]) and percent epithelialization.

8.R Outline of the review conducted by PMDA

PMDA's view on post-marketing use-results survey plan:

The applicant's explanation ("The observation period will begin at the time of tissue harvest for the production of JACE and end at 16 weeks after grafting. This period was selected assuming that the skin has undergone 2 cycles of turnover after graft take. The observation is intended to assess epithelialization after JACE grafting and stability after epithelialization) is understandable. The proposed observation period up to 16 weeks after grafting is appropriate in terms of efficacy evaluation of JACE. There were no major problems with study procedures or the safety or tolerability of JACE in Studies J-TEC-EB and J-TEC-01-01. No adverse events possibly related to the procedures of Study J-TEC-01-01 or JACE occurred at ≥16 weeks after JACE grafting in Study J-TEC-01-01 and the subsequent follow-up clinical research (an interim report up to the data cutoff date at ≥1 year after the end of follow-up period of Study J-TEC-01-01). Thus, also from the viewpoint of safety evaluation, the observation period up to 16 weeks after grafting is appropriate. Although the applicant proposed that the clinical course after the initial grafting only should be observed, the clinical course after re-grafting should also be observed. This is because the same site may be re-grafted with JACE if adequate epithelialization does not occur after grafting or if the percent epithelialization is reduced after grafting. When

re-grafting with JACE is performed, information on the efficacy and safety of JACE should be collected by grafting procedure (up to 16 weeks after the last grafting). Also when multiple sites are grafted with JACE in serial procedures, each graft recipient site should be observed up to 16 weeks after the last grafting.

Furthermore, as to the survey item of "information on the success or failure of JACE production," the cause of failure of JACE production after tissue harvest should be investigated. In order to investigate the possible association of the success or failure of JACE production with the general condition of the patient [see Section 7.R.5], clinical laboratory tests should be included in the survey items. Key survey items proposed by the applicant are appropriate.

Information on the safety of JACE in the treatment of intractable or recurrent erosions/ulcers in patients with EB is very limited. The applicant should therefore provide healthcare professionals with the safety information obtained from post-marketing use-results survey of JACE, as needed, and take appropriate and prompt action, for example, by taking further safety measures, if necessary.

The details of post-marketing use-results survey will be finalized, taking also account of discussion about efficacy and safety evaluation of JACE at the Expert Discussion.

9. Results of Compliance Assessment Concerning the Application Data and Conclusion Reached by PMDA

9.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Review Report (2).

9.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing, and its results and PMDA's conclusion will be reported in the Review Report (2).

10. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that JACE has a certain level of efficacy in the treatment of intractable or recurrent erosions/ulcers in patients with dystrophic EB and is expected to have efficacy in the treatment of intractable or recurrent erosions/ulcers in patients with junctional EB, and that JACE has acceptable safety in view of its benefits. Making JACE available for clinical use as a new option for the treatment of EB is of significance.

PMDA has concluded that JACE may be approved for the new indication if JACE is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 2, 2018

Product Submitted for Partial Change Approval

Brand name	JACE
Non-proprietary name	Human (autologous) epidermal cell sheet
Applicant	Japan Tissue Engineering Co., Ltd. (J-TEC)
Date of application	March 20, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

PMDA's conclusion:

In view of the considerations presented in Section "7.R.1 Efficacy" in the Review Report (1), the results from Studies J-TEC-EB and J-TEC-01-01 and Japanese clinical research demonstrated a certain level of efficacy of JACE in the treatment of patients with dystrophic EB. However, since the currently available information on the efficacy of JACE is very limited, the applicant should further collect post-marketing information on the efficacy of JACE.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.2 Safety

PMDA's conclusion:

PMDA reviewed adverse events reported in Studies J-TEC-EB and J-TEC-01-01 and Japanese clinical research. There are no major differences in the safety profile of JACE between EB and the previously approved indications. No new clinically relevant adverse events of special interest have occurred in patients with EB.

However, 1 subject had skin ulcer at the donor site (unresolved) in Study J-TEC-EB. Given the pathology of EB, ulcers are likely to occur at the donor site and may be persistent in EB patients as compared to the previously approved indications. Thus, the "Important Precautions" section of the package insert should advise

that attention should be paid to the possible occurrence of skin ulcer in patients with EB, for example, by observing the donor site periodically.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.3 Indication or performance

PMDA's conclusion:

In view of the considerations presented in Section "7.R.3 Clinical positioning and indication or performance" in the Review Report (1), the indication or performance statement should be "dystrophic epidermolysis bullosa and junctional epidermolysis bullosa; JACE is indicated for the treatment of intractable or recurrent erosions/ulcers in patients with dystrophic or junctional epidermolysis bullosa. The cultured epidermal cell sheet is applied onto an intractable or recurrent erosion/ulcer to promote epithelialization." The "Precautions for Indication or Performance" section of the package insert should include the statement that "JACE should be used to treat an erosion or ulcer of approximately 4 weeks' duration or an erosion or ulcer characterized by repeated cycles of ulceration and re-epithelialization."

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA. Based on the discussion at the Expert Discussion, PMDA concluded that the appropriate statements in the "Indication or Performance" and "Precautions for Indication or Performance" sections should be as shown below.

Indication or Performance

3. Dystrophic epidermolysis bullosa and junctional epidermolysis bullosa

JACE is indicated for the treatment of intractable or recurrent erosions/ulcers in patients with dystrophic or junctional epidermolysis bullosa. The cultured epidermal cell sheet is applied onto an intractable or recurrent erosion or ulcer to promote epithelialization.

Precautions for Indication or Performance

- JACE should be used to treat an erosion/ulcer of approximately 4 weeks' duration or an erosion/ulcer characterized by repeated cycles of ulceration and re-epithelialization.

PMDA instructed the applicant to include the above statements in the "Indication or Performance" and "Precautions for Indication or Performance" sections. The applicant responded to the instruction appropriately, and then PMDA accepted it.

1.4 Dosage and administration or method of use

Taking account of dosage and administration or method of use, etc., employed in Studies J-TEC-EB and J-TEC-01-01, PMDA concluded that the proposed dosage and administration or method of use and associated precautions should be handled as follows:

- In view of the considerations presented in Section "7.R.4.1 Tissue harvest" in the Review Report (1), skin tissue for the production of JACE should be taken from normal-appearing areas. As long as reference

information to select the donor site is communicated appropriately to healthcare professionals in clinical practice, no other conditions are necessary.

- In view of the considerations presented in Section "7.R.4.2 Treatment before JACE grafting" in the Review Report (1), the "Dosage and Administration or Method of Use" section of the package insert should advise that the wounds should be treated appropriately with debridement, saline irrigation, etc., as necessary, before JACE grafting.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

In the regulatory review of the initial application for JACE for severe burns, the safety of process-related impurities following grafting of 200 pieces of JACE sheets (the assumed maximum number of JACE to be grafted in serial procedures) was evaluated, and the maximum number of JACE to be grafted in serial procedures was specified in the "Dosage and Administration or Method of Use" section [see Section "4. Electrical safety, biological safety, and other safety-related data" and Section "6. Clinical data" in the Review Report (1) for the initial approval of JACE]. Considering that re-grafting of JACE may be necessary due to recurrent ulcers, etc. in patients with EB, PMDA asked the applicant to explain the expected total number of JACE sheets required for the treatment of EB and its safety.

The applicant's explanation:
EB is a congenital, genetic disease, and the disease condition develops shortly after birth. If the patient is re-grafted with JACE continuously, the total number of JACE sheets grafted will exceed 200. However, the applicant's current view on the safety of process-related impurities in JACE is as follows:
The local safety of process-related impurities at the graft recipient sites, including the cases of re-grafting, has been demonstrated in Studies J-TEC-EB and J-TEC-01-01 and clinical experience in the treatment of severe burns and giant congenital melanocytic nevi. Although antibiotics are process-related impurities to which the body may be exposed through the graft recipient site and which may have systemic effects, only trace amounts of residual antibiotics are present in JACE, relative to their approved doses as pharmaceutical products. Even if the total number of JACE sheets grafted in serial procedures exceeds 200, there will be no safety concerns regarding the accumulation of residual antibiotics.

PMDA accepted the applicant's explanation and concluded that the maximum number of JACE sheets to be grafted in serial procedures (200 sheets) specified in the "Dosage and Administration or Method of Use" section can be deleted.

1.5 Qualifications of medical institutions and surgeons/physicians for using JACE

In view of the considerations presented in Section "7.R.6 Qualifications of medical institutions and surgeons/physicians for using JACE" in the Review Report (1), PMDA concluded that JACE should be used by surgeons/physicians and at medical institutions meeting the following requirements.

- Medical institutions are required to have facilities and staff necessary to provide postoperative management.
- JACE should be appropriately handled by specialists with adequate knowledge, skills, and experience in treatment of EB; specifically, dermatologists, plastic surgeons, or pediatricians.
- Treating surgeons/physicians should be informed and trained through written materials etc., which describe the nature of JACE, grafting procedure, treatment before and after grafting, precautions for use, etc.

At the Expert Discussion, the expert advisors largely supported the above conclusion by PMDA, but made the following comment on the qualifications of surgeons/physicians: Since EB is a very rare disease, the involvement of a dermatologist should be mandatory in terms of adequate experience in the diagnosis and treatment of EB.

PMDA's conclusion:

The qualifications of surgeons/physicians to use JACE should be modified to state that the involvement of a dermatologist be mandatory. Specifically, the use of JACE by non-dermatology specialists (e.g., plastic surgeons, pediatricians) requires cooperation with a dermatologist.

PMDA instructed the applicant to redefine the qualifications of medical institutions and surgeons/physicians to use JACE. The applicant responded to the instruction appropriately, and PMDA accepted it.

1.6 Post-marketing use-results survey plan (draft)

Based on the considerations presented in Section "8.R Outline of the review conducted by PMDA" in the Review Report (1), PMDA concluded as follows:

- The survey should include all patients who undergo tissue harvest for the production of JACE during the re-examination period.
- The observation period should be up to 16 weeks after grafting in terms of efficacy and safety evaluation of JACE.
- Although the applicant proposed that the clinical course after the initial grafting only should be observed, the clinical course after re-grafting should also be observed. This is because the same site may be re-grafted with JACE if adequate epithelialization does not occur after grafting or if the percent epithelialization is reduced after grafting. When re-grafting with JACE is performed, the efficacy and safety of JACE should be evaluated by grafting procedure (up to 16 weeks after the last grafting).
- When multiple sites are grafted with JACE in serial procedures, each graft recipient site should be observed up to 16 weeks after the last grafting.
- As to the survey item of "information on the success or failure of JACE production," the cause of failure of JACE production after tissue harvest should be investigated.
- In order to investigate the possible association of the success or failure of JACE production with the general

condition of the patient, clinical laboratory tests should be included in the survey items.

- Key survey items proposed by the applicant are appropriate.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

PMDA instructed the applicant to review the use-results survey plan, taking account of the above points. The applicant presented an outline of a revised use-results survey plan (draft) as shown in Table 8, and PMDA accepted it.

Table 8. Outline of post-marketing use-results survey (draft)

Objective	To assess the safety etc. of JACE in routine clinical practice.
Survey method	All-case surveillance
Population	Patients with dystrophic or junctional EB
Observation period	16 weeks after the last grafting of JACE for each graft recipient site
Target sample size	All patients who undergo tissue harvest for the production of JACE during the re-examination period
Survey items	**Patient characteristics** 1) Date of birth 2) Sex 3) Height, body weight 4) Target disease (type of EB [including information on dystrophic or junctional EB and dominant or recessive inheritance pattern]) 5) Complications 6) Previous illnesses 7) Information on tissue harvest (anatomic site, donor site size, description, and the results of rub test with ballpoint pen[9)] if the test is performed to assess resistance to mechanical stress) 8) Clinical laboratory tests (hematology and clinical chemistry) 9) Concomitant medications/therapies **Safety** 1) Adverse events 2) Clinically significant adverse reactions (neoplastic lesions at the graft recipient site that were considered possibly related to JACE grafting, allergic symptoms that were considered possibly related to JACE grafting cannot be ruled out, unknown infections of unknown cause that were considered possibly related to JACE grafting) 3) Malfunctions **Efficacy** 1) Percent epithelialization (%) 2) Objective symptoms (blisters/ulcers) **Other survey items** 1) Information on the success or failure of JACE production
Key survey items	1) Percent epithelialization (%) 2) Clinically significant adverse reactions (the events that were considered possibly related to JACE grafting [neoplastic lesions at the graft recipient site, allergic symptoms, unknown infections of unknown cause])

9) With a quick movement, the tip of a retracted ballpoint pen is pushed over the skin for a distance of 2 to 4 mm, for skin fragility assessment (*J Invest Dermatol.* 2014; 134: 2097-104).

2. Results of Compliance Assessment Concerning the Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The application data (Attached document 1, Attached document 2) were subjected to an on-site GCP[10)] inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication or performance and dosage and administration or method of use shown below, with the following conditions. This application has been filed for an orphan regenerative medical product. The re-examination period for the indication or performance claimed in the present application is 10 years.

Indication or Performance

1. Severe burns

JACE is indicated for use in patients with serious, extensive burns when sufficient donor sites for autologous skin grafts are not available and the total area of deep dermal and full-thickness burns is 30% or more of the total body surface area. A cultured epidermal cell sheet is applied onto the reconstructed dermis in a full-thickness burn wound to facilitate the closure of the wound. Dermis should be reconstructed with allografts, as a general rule. JACE should be used for deep dermal burn wounds only when full-thickness and deep dermal burns coexist and it is difficult to treat them separately.

2. Giant congenital melanocytic nevi

The cultured epidermal cell sheet is applied onto a wound after excision of giant congenital melanocytic nevi to facilitate the closure of the wound.

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10) Although the present application was filed under the category of regenerative medical products, the clinical study (Attached document 1) had been conducted before the enforcement of the Ministerial Ordinance on GCP for Regenerative Medical Products. Therefore, the Ministerial Ordinance on GCP for Medical Devices was applicable to this clinical study.

3. Dystrophic epidermolysis bullosa and junctional epidermolysis bullosa

JACE is indicated for the treatment of intractable or recurrent erosions/ulcers in patients with dystrophic or junctional epidermolysis bullosa. The cultured epidermal cell sheet is applied onto an intractable or recurrent erosion/ulcer to promote epithelialization.

(Underline denotes additions.)

Dosage and Administration or Method of Use

Grafting plan

1. Grafting plan

A treating surgeon/physician develops a grafting plan and provides the manufacturer of JACE with the details of the plan, which consist of the number of cultured epidermal cell sheets required, the dates of tissue harvest and grafting, the number of grafting procedures, and other necessary information such as on the medical institution and the patient (hereinafter collectively referred to as the "grafting planning information"). The manufacturer prepares an order form indicating a tissue code unique to each grafting plan and the grafting planning information, then send it to the treating surgeon/physician.

The treating surgeon/physician confirms the grafting planning information entered in the order form sent by the manufacturer, before placing an order for production of JACE.

The manufacturer supplies the surgeon/physician with a tissue transport kit (comprising tissue transport tubes) and a dedicated heat-insulating container in time for the date of tissue harvest. The tissue code is indicated on the carton of the tissue transport kit, tissue transport tubes, and heat-insulating container for tissue transportation provided by the manufacturer.

Tissue code

Tissue codes are issued for each grafting plan.

For a patient undergoing tissue harvest more than once, each piece of tissue harvested is identified by a unique tissue code. A grafting plan is developed on a tissue-code basis.

For a patient undergoing a single tissue harvest followed by serial grafting procedures, cultured epidermal cell sheets for multiple grafting procedures are produced using cells derived from the same skin tissue. The tissue code remains unchanged for production of such sheets. Therefore, these sheets are identified with the same tissue code and different batch numbers.

Steps from tissue harvest at the medical institution through the receipt of harvested tissue

2. Tissue harvest

Skin tissue is harvested based on the size of the graft recipient site and according to the grafting plan. The harvested skin should be at least 1 cm^2 in size and elliptical in shape or in such a shape that allows for easier

suture. Skin tissue is taken from lesion-free normal skin at any anatomical site. The full-thickness of dermis should be harvested from the donor site.

3. Storage of harvested tissue

The sealing band on the heat-insulating container is cut with scissors to remove the lid and take out the tissue transport kit. The tissue code indicated on the heat-insulating container, carton of the tissue transport kit, and tissue transport tubes is checked against the order form.

The tissue transport kit is unsealed in a clean environment (e.g., operating room, procedure room) to take out the transport tube. The tube is checked for leakage and turbidity of the medium filled in it. If the medium is turbid, the spare tube is used.

The tissue transport tube should not be tilted or shaken unnecessarily.

The tissue transport tube is uncapped. The skin tissue, harvested in a clean environment, is placed in the tube using sterile forceps, etc. to be immersed in the medium. The tube is then capped tightly to prevent a leak of the medium. The date of tissue harvest and the name of the person who performed harvest are indicated on the tube.

4. Transportation of harvested tissue

The tissue transport tube is placed in the carton. The carton is sealed for tamper resistance and placed in the heat-insulating container (temperature during transportation, 4°C to 25°C). The container is sealed with 4 sealing bands for delivery to the manufacturer. The manufacturer should receive the skin tissue within 62 hours after the heat-insulating container has been shipped to the medical institution [see “1. Grafting plan”].

Note: Presumably, each medical institution will follow its own procedure for handling harvested skin tissue and JACE (e.g., special procedures, responsible department). Therefore, the distributor will undertake the transportation of harvested skin tissue and JACE under the supervision of the manufacturer until a reliable system is established and maintained for the delivery and acceptance of harvested skin tissue and JACE. Once such a system is fully in place, part of the transportation process will be outsourced to a logistics company while the distributor will still be responsible for the rest of the process.

Steps from release at the manufacturer through acceptance at the medical institution

5. Acceptance inspection and handling of the product at the medical institution

(1) A package of cultured epidermis is shipped in a heat-insulating container sealed with bands. The medical institution must ensure that the container is kept sealed before use.

The heat-insulating container is unpacked by cutting the sealing bands with scissors to take out the package of cultured epidermis.

(2) The tissue code (5-digit alphanumeric code) incorporated in the batch number on the package is checked against the order form retained at the medical institution (issued in the step as described in "1. Grafting plan"). The number of the cultured epidermal cell sheets is checked.
(3) The package of cultured epidermis is stored at 10°C to 25°C until immediately before use.

Grafting

6. Procedures before grafting of the cultured epidermal cell sheet

(1) Severe burns

Dermal reconstruction is performed on the site to be treated with the cultured epidermal cell sheet.

(2) Giant congenital melanocytic nevi

The lesion (nevus) is excised. The surgical technique for excision is determined according to the patient's age and nevus size. Dermal reconstruction is performed as necessary.

(3) Dystrophic epidermolysis bullosa and junctional epidermolysis bullosa

The patient's intractable or recurrent erosion/ulcer is treated appropriately with debridement, saline irrigation, etc., as necessary.

7. Grafting of the cultured epidermal cell sheet

(1) Severe burns

The cultured epidermal cell sheet is applied onto the reconstructed dermis. However, the grafting should be preceded by appropriate wound bed preparation such as the removal of necrotic tissue or other factors that render the recipient wound bed unsuitable for grafting, if any.

The cultured epidermal cell sheet may be used on a deep dermal burn wound only when full-thickness and deep dermal burns coexist and it is difficult to treat them separately.

(2) Giant congenital melanocytic nevi

The cultured epidermal cell sheet is applied onto the preserved dermis or reconstructed dermis of a wound after nevus excision.

(3) Dystrophic epidermolysis bullosa and junctional epidermolysis bullosa

The cultured epidermal cell sheet is applied onto the appropriately pre-treated intractable or recurrent erosion/ulcer.

8. The maximum number of cultured epidermal cell sheets to be grafted in a single procedure

Up to 50 pieces of cultured epidermal cell sheets are allowed to be grafted in a single procedure~~, and a total of up to 200 cell sheets in serial procedures~~. ~~The number of cultured epidermal cell sheets used should not exceed these upper limits.~~

(Underline denotes additions/changes and strikethrough denotes deletions.)

Conditions of Approval

1. Because the clinical studies were conducted in extremely limited number of subjects, the applicant is required to conduct a use-results survey covering all patients treated with the product. As a rule, the survey should be continued until the end of the re-examination period. New efficacy and safety data on the product should be communicated appropriately to surgeons/physicians and medical institutions providing treatment with the product, and patient information materials should be updated with the data accordingly.
2. Due to the risks associated with xenotransplantation of 3T3-J2 cells derived from mouse embryo, which are used as feeder cells in the manufacture of the product, the applicant is required to take necessary measures to ensure appropriate handling, such as 30-year retention of a sample of the finished product and a record of use.

List of Abbreviations

COL7A1	Collagen type VII alpha 1 chain
COL17A1	Collagen type XVII alpha 1 chain
EB	Epidermolysis bullosa
FAS	Full analysis set
LAMA3	Laminin subunit alpha 3
LAMB3	Laminin subunit beta 3
LAMC2	Laminin subunit gamma 2
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per protocol set
The product	JACE