Provisional Translation (as of January 2026).
This English document has been prepared for reference purpose only. In the event of inconsistency and discrepancy between the Japanese original and the English translation, the Japanese text shall prevail.

(Attachment 1)

Guidance on evaluation of autologous iPS cells derived retinal pigment epithelial cells

1. Introduction

Basic technical requirements for ensuring quality and safety of drugs or medical devices obtained by processing human-derived autologous induced pluripotent stem cells (iPS cells) or induced pluripotent stem-like cells (iPS-like cells) (hereinafter referred to as "Human (autologous) iPS (-like) cell processed products") are defined in the "Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell and Tissue (Autologous iPS (-like) cells)" (PFSB Notification No. 0907-4, dated September 7, 2012, of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare [MHLW]).

The guidance on evaluation provides, in addition to the above basic technical requirements, points to consider specific to a particular class of human (autologous) iPS cell processed products that are used as medical devices applied for treatment of retinal pigment epithelial disorders, etc.

2. Scope of the guidance on evaluation

The guidance on evaluation provides, in addition to the basic technical requirements, points to consider for evaluation of quality, efficacy, and safety of a particular class of human (autologous) iPS cell processed products that are used as medical devices applied for treatment of retinal pigment epithelial disorders, etc.

If having difficulty determining whether the product to be developed is classified as a medical device, the applicant should consult with the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW.

3. Positioning of the guidance on evaluation

The guidance on evaluation, which applies to medical devices, a particular class of human (autologous) iPS cell processed products currently undergoing remarkable development of technologies, provides only points to consider at the present time, but does not intend to cover considerations comprehensively. It is supposed to be revised in response to further technological innovation and accumulation of knowledge and thus not binding on application data.

Product evaluation requires scientifically rational flexibility with full understanding of characteristics of individual products.

In addition to the guidance on evaluation, other related guidelines in and outside Japan should be referred to.

4. Definitions of terms

Terms used in the guidance on evaluation are as defined in the "Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell and Tissue (Autologous iPS (-like) cells)" (PFSB Notification No. 0907-4, dated September 7, 2012, of the Pharmaceutical and Food Safety Bureau, MHLW) or defined as follows.

(1) Retinal pigment epithelial cells: The term refers to cells forming the outermost layer of the 10-layer retina. They are epithelial cells forming a monolayer, phagocytose photoreceptor cells, produce visual pigments such as retinal, and constitute the blood retinal barrier. A primary lesion of age-related macular degeneration occurs involving the cells.

(2) Photoreceptor cells: The term refers to one type of cells constituting the retina. Photoreceptor cells can be simply called photoreceptors and convert light energy into electrical energy. Located in the outermost layer of the neuroretina, the tip part called the outer segment is constantly phagocytosed by the retinal pigment epithelial cells, being replaced with a new outer segment.
(3) Phagocytotic capacity: Retinal pigment epithelial cells, like macrophages, are capable of ingesting foreign substances (e.g., bacteria, cellular debris) into their own cells and digesting them. In a normal state, they intake the tip part of photoreceptor cells constantly.
(4) Barrier function: Retinal pigment epithelial cells are bound via an adhesive structure to each other, not allowing substances to move freely. This function is called barrier function.
(5) Cell sheet: The term refers to a sheet formed by cells, which are bound to each other.
(6) Subretinal transplantation: The term refers to a surgical treatment in which tissues, instruments, etc. are inserted in a space intentionally made in the subretinal cavity (between the sensory retina and retinal pigment epithelial cells).
(7) Exudative lesion: The term refers to a pathological site of choroidal neovascularization associated with age-related macular degeneration. Subretinally accumulating exudate or neovascular tissue in this lesion disturbs the retinal structure, causing a rapid and severe decrease in visual acuity.
(8) Ophthalmoscopy: The term refers to an examination in which the fundus is exposed to light inserted from the front of the eyeball through the pupil and observed for changes in the retina and choroid using an indirect ophthalmoscope, retinoscope, direct ophthalmoscope, etc.
(9) Fluorescein angiography: The term refers to observation and photography examination of the fundus after intravenous administration of a fluorescent substance (e.g., fluorescein) using a specialized camera. The examination allows assessment of hemodynamics in the fundus and barrier function as well as detection of neovessels.
(10) Optical coherence tomography: The term refers to examination allowing observation of living retina's cross-sections and is abbreviated to OCT This modality excels in detecting choroidal neovascularization, retinal detachment, etc.
(11) Retinal sensitivity test: The term refers to a test that examines the visual field of a subject by projecting small lights of varying brightness on different points of the retina. The test can be performed by microperimetry or static perimetry.

5. Points to consider for evaluation

(1) Quality control of products

[1] Characterization Items for establishment of quality specifications for retinal pigment epithelial cells

a) Shape

Cell morphology specific to retinal pigment epithelial cells (e.g., brown pigment, polygonal and cobblestone-like cell form) should be confirmed under a phase contrast microscope, etc.

b) Expression of genes characteristic of retinal pigment epithelial cells

Expression of genes related to retinal pigment epithelium (e.g., RPE65, CRALBP, MERTK, BEST1) should be confirmed.

c) Purity

Purity of the product should be determined by immunostaining using multiple antibodies against RPE65, bestrophin, PAX6, etc. Of cells that are obtained from pure

culture based on the related gene expression and have the characteristic morphology, ones containing pigment are mostly deemed as retinal pigment epithelial cells. Purity may be determined from the count of cells containing pigment objectively quantified by image processing, etc.

d) Absence of undifferentiated cells

According to literature, presence of undifferentiated cells may be assessed by flow cytometry in combination with immunostaining of undifferentiated cell markers (OCT3/4, Sox2, TRA-1-60) or by quantification of marker genes by quantitative reverse transcription (RT)-PCR (assessment based on expression levels of genes such as OCT3/4, NANOG, and LIN28, determined by a one-step 45-cycle quantification regimen, etc.). Of the marker genes, LIN28 gene is highly specific to undifferentiated cells and provided with a highly sensitive quantitative analysis, which can be commonly used as a representative assessment method (Reference data 1).

It should be noted that presence of undifferentiated iPS cells does not necessarily lead to tumorigenicity. For tumorigenicity studies, the nonclinical study section should be referred to.

e) Functions

To confirm that the produced cells have functional properties of retinal pigment epithelial cells consistent with the intended treatment use, the in-process product should be analyzed. The following functions may be tested.

- Phagocytotic capacity (intracellular uptake of fluorescence-labeled photoreceptor outer segments, fluorescent beads, etc., which were added to a culture medium, is assessed by flow cytometry, etc.)
- Secretion capacity of growth factors (amounts of vascular endothelial growth factor [VEGF], pigment epithelium-derived factor [PEDF], etc. secreted are determined by enzyme-linked immunosorbent assay [ELISA]).

[2] Characterization Items for establishment of quality specifications for retinal pigment epithelial cell sheet

Before characterization of a retinal pigment epithelial cell sheet, the shape, mechanical suitability, and functional properties should be evaluated as described below, and the manufacturing process of the sheet should be justified as well.

a) For shape, for example, preparation of tissue sections of the sheet or 3-dimensional observation under a confocal microscope should be performed to confirm that the cells form a sheet.

b) For mechanical suitability, after operations ranging from removal of the cell sheet to preparation of a graft, whether the graft is intact as the sheet should be checked.

c) To evaluate functional properties (barrier function), an analysis on expression of appropriate markers reported to correlate with barrier function, which are identified by immunostaining (using antibody against ZO-1), etc. or trans epithelial electrical resistance (TEER) measurement should be performed.

(2) Nonclinical studies

[1] Tumorigenicity studies

For validation of the manufacturing process, where possible, final products that have been manufactured using at least 3 lines from different donors by the same process and meet the same quality criteria should be used in tumorigenicity evaluation using a study system in immunodeficient animals with the known detection sensitivity. If the final products are locally (subretinally or subcutaneously) administered to a certain number of sites for the evaluation

using such system, useful information will be obtained. Tumorigenicity should be comprehensively analyzed by a soft agar medium assay, karyotyping, etc. if necessary and scientifically justified. However, the above tumorigenicity evaluation methods may warrant revision depending on data to be accumulated in future clinical applications.

Based on the general concept of nonclinical safety evaluation including tumorigenicity studies, in principle, safety of the final product should be evaluated separately from that of source materials (iPS cells). In nonclinical studies of retinal pigment epithelial cells derived from autologous iPS cells, etc. overall, functionally matured retinal pigment epithelial cells are used. Thus, if retinal pigment epithelial cells have been adequately investigated in terms of points to consider for evaluation in the guidance on evaluation and fully characterized, final products can be considered to have comparable nonclinical safety irrespective of minor changes to donors, lines, and manufacturing method.

[2] Primary efficacy or performance studies

Because almost functionally matured retinal pigment epithelial cells are to be transplanted, subretinal transplantation should be performed in retinal degeneration animal models such as Royal College of Surgeons rats (RCS rats) in principle to evaluate the protective effect of retinal pigment epithelial cells on the retina.

[3] Others

If a special procedure is required for sheet insertion, etc., items deemed necessary and scientifically valid for clinical application, such as safety of the procedure and acute local reactions to the procedure after transplantation, should be investigated in medium- or large-sized animals where possible.

(3) Clinical studies (clinical trials)

[1] Indication

Diseases adversely affecting retinal pigment epithelium

Age-related macular degeneration, degenerative myopia, Stargardt disease, trauma, retinitis pigmentosa, etc.

[2] Systemic monitoring items

Subjects should undergo systemic screening for malignant tumor before transplantation wherever possible, because if a tumor is found outside the eye after transplantation, whether it is derived from the transplanted cells must be determined. Attention should be paid to tumor development, etc. for an appropriately pre-determined period of time after transplantation procedure.

[3] Assessment methods of transplantation treatment

Effects of the treatment of the disease subject to the guidance on evaluation can be evaluated mainly by 2 approaches presented in a) and b) below, anatomical and visual function-based assessments. Which approach should be used for endpoints at which time point should be specified as appropriate depending on the target disease and details of the treatment. For comparison, control data should be obtained from treatment results in past reports or control groups used in these reports as appropriate according to the design of a clinical study. The clinical study may enroll, for example, patients who have not adequately responded to the conventional treatment (e.g., anti-VEGF therapy for age-related macular degeneration) or those who meet certain criteria irrespective of response to the existing treatment. If the target disease is a type of disease that progresses bilaterally such as hereditary degenerative disease, the untreated opposite eye should be used as a control.

The current assessment flow in the field of ophthalmology is summarized below. Because ophthalmological examination technologies are rapidly advancing, assessment methods that are considered valid and appropriate for the study at that time should be used if possible.

a) Anatomical assessment

Ophthalmoscopy, diagnostic imaging (e.g., fluorescein angiography, optical coherence tomography), etc.

In recent years, diagnostic imaging technologies for ophthalmological examinations are remarkably advancing. For example, optical coherence tomography (OCT) is an examination technology highly useful and reliable in evaluating the protective effect on the retina over time objectively, because it is non-invasive and provides detailed and high-resolution cross-section images of the fundus, which give information about presence or absence of an active exudative lesion associated with age-related macular degeneration and actual quantitative status of residual photoreceptor cells including those affected by dry-type after treatment. Use of diagnostic imaging technologies such as OCT is the optimum approach to assess survival and effectiveness of transplanted cells. For safety evaluation, fluorescein angiography and OCT are appropriate because these technologies are considered to provide data of the highest sensitivity, including information about rejection and tumorigenesis.

b) Visual function examination

Visual acuity, retinal sensitivity, perimetry, electrophysiological examinations, etc.

Pigment epithelial disorders in the macular area and secondary exudative age-related macular degeneration can be accompanied by exudative pathological conditions such as choroidal neovascularization, which gradually progress degeneration of photoreceptor cells in the overlying macular area. The visual function depends on the condition of photoreceptor cells. The primary objective of transplantation treatment is to prevent visual dysfunction (decreased visual acuity) of the macular area, which is inevitable after onset of these diseases, at the earliest possible time and to protect the remaining photoreceptor cell function by supplementing the healthy pigment epithelium to the macular area. Basically, restoration of the lost photoreceptor cells is impossible at the present time, and thus it does not suit to the objective of this treatment.

Although central visual acuity is commonly used as an indicator representative of the visual function, it is affected by the position of remaining healthy visual cells in the central region in the strict sense. That is, the more photoreceptor cells closer to the central region remain, the better the visual acuity is kept. In age-related macular degeneration, etc., however, in a sense, photoreceptor cells are lost in a random and disordered manner, but not in a concentric and uniform manner. To what extent photoreceptor cells remain in the macular area does not necessarily correlate with visual acuity. Visual functions based on subjective perception differ among individuals. (the following discrepancy cases actually occur: “I see numeric characters presented at a visual acuity test but cannot not perceive them”; and “My visual acuity is numerically low, but I live more comfortably than generally thought.”)

Treatment given at the earlier stage of a disease can protect more photoreceptor cells closer to the central region and thus generally keep visual acuity unimpaired.

Treatment at the advanced stage of a disease, on the other hand, cannot be expected to improve visual acuity because photoreceptor cells in the central region have been already lost. However, if treatment protects intact photoreceptor cells surrounding the lesion, improvement such as a reduction in central scotoma (central blind spot) can be achieved.

Thus, visual function-based assessment should be comprehensively performed according to the stage of the target disease if possible, including retinal sensitivity or indicators related to response at a further local point in the macular area such as central vision and the extent, besides visual acuity in cases where assessment only based on visual acuity is considered inappropriate.

If the target disease is eligible for local analyses, electrophysiological examinations may be a favorable indicator as objective visual function tests.

If treatment is given to the dominant eye in patients with bilateral eye disease, measures of vision-related quality of life (QOL) such as NEI VFQ-25 can be an indicator to assess visual functions (Reference data 2).

6. Reference data

1. Kuroda T, Yasuda S, Kusakawa S, Hirata N, Kanda Y, Suzuki K, Takahashi M, Nishikawa S, Kawamata S, Sato Y. Highly sensitive in vitro methods for detection of residual undifferentiated cells in retinal pigment epithelial cells derived from human iPS cells. PLoS One.2012;7(5):e37342.
2. Orr P, Rentz AM, Marfolis MK, Revicki DA, Dolan CM, Colman S, Fine JT, Bressler NM. Validation of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) in age related macular degeneration Invet. Ophthalmol. Vis Sci.2011; 52:3354-3359.

(Attachment 2)

Guidance on Evaluation of Devices for Restoration of Motor Functions

1. Introduction

Attempts to use robotic devices for restoration of motor functions in the field of rehabilitation have been globally. To ensure that the robot technology, in which Japan excels, is put into practical and widespread use and thereby benefits the public, safety of the devices and their medical effectiveness in clinical settings as well as research results on new technological aspects must be evaluated.

Aims of introduction of devices for restoration of motor functions into the field of rehabilitation are to derive quantitative information on motor functions from the knowledge conventionally accumulated via therapists' trained sense, based on operational theories of the devices; to realize quantitative output of the devices based on the derived information; to improve efficiency of rehabilitation by increasing the reproducibility and accuracy; and to reduce burden on healthcare professionals such as therapists.

The guidance on evaluation provides points to consider for proper and prompt evaluation of safety and efficacy of devices for restoration of motor functions based on scientific evidence.

2. Scope of the guidance on evaluation

The guidance on evaluation applies to devices for restoration of motor functions including hardware and software that restore the motor functions impaired by disease. In other words, the guidance on evaluation applies to devices that deliver motor output through actuators based on surrounding environment and input from their own sensors and are expected to finally improve motor functions, mainly for motor control for extremities and trunk. In addition, the preceding guidance on evaluation for neuromodulation devices (Attachment 2 to PFSB/ELD/OMDE Notification No. 1215-1, dated December 15, 2010, of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare [MHLW]).

In the guidance on evaluation, devices for restoration of motor functions refer to devices that formulate basic operational theories and quantify activity information data and are used in living space such as hospitals, facilities, and home not only to restore physical and cognitive functions and physical structures but also to aid individuals in doing activities of living and participating in societies and thereby improve living functions ultimately.

If having difficulty determining whether the device for restoration of motor functions to be developed is classified as a medical device, the applicant should consult with the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW where necessary.

3. Positioning of the guidance on evaluation

The guidance on evaluation, which applies to the medical devices currently undergoing remarkable development of technologies, provides only points to consider at the present time, but does not intend to cover considerations comprehensively. It is supposed to be revised in response to further technological innovation and accumulation of knowledge and thus not binding on application data. Product evaluation requires scientifically rational flexibility with full understanding of characteristics of individual products. In addition to the guidance on evaluation, other related guidelines in and outside Japan should be referred to.

4. Points to consider for evaluation

(1) Basic matters

[1] Development history, product specifications, use in and outside Japan, design development and principle of the device, mechanism of action related to performance and efficacy, intended method of use, etc. (including functions and abilities) should be clearly described.

[2] Risk assessment should be performed in view of the installation location, operation, etc. of the device, and appropriate precautions, etc. should be specified with reference to the following items.

(a) Installation
- Weight
- Dimensions
- Measures to prevent the device from falling over
- Burden on the body site of contact with the device (e.g., compression, displacement, burn)

(b) Noise and vibration of the device
(c) Necessity of maintenance and inspection and the details
(d) Necessity of training program and the details
(e) Safety measures for power supply and drive units (e.g., necessity of backup power supply unit, load on drive control unit, time available for continuous drive, time taken to attach the device to a patient)
(f) Measures for surrounding environment (e.g., electromagnetic waves, temperature)
(g) Use environment (e.g., hospital, facility, home.)

(2) Nonclinical studies

Performance and safety of the device should be evaluated appropriately through the following items, etc.

[1] Performance

For each of the following matters, applicable items should be clarified with specific data.

(a) Performance of moving parts
- Drive system (e.g., active system, passive system)
- Control method (e.g., force control, position control, impedance control, compliance control, presentation control)
- Backdrive ability (e.g., driving force transmission mechanism between grips and actuators)
- Operational accuracy (e.g., positional/spatial accuracy, temporal accuracy [including time delay], reproducibility, validation method)
- Structure and functions of sensors (e.g., position, angle, biological signal)
- Validity of precision (e.g., correlation with operational accuracy required for cases applicable to the indication)
- Operating distance, speed
- Output of actuator, etc. (including the upper limit)
- Degree of freedom of movement
- Spatial arrangement (e.g., interference with other devices, users, patients)

(b) Display of operation status of the device
(c) Durability (including measures against corrosion, heat generation)
(d) Software life cycle management
(e) Self-diagnosis function (including validation of operational accuracy described above)

[2] Safety and quality

The following items for design control should be applied as necessary.

(a) General requirements
- Electrical safety
- Mechanical safety
- Biological safety
- Quality management
- Risk management

(b) Specifications (including drive units)
- Design requirements (users, standards, regulations, standards)
- Input and output (e.g., type, method, means)
- Usability
- Startup, interruption, and termination

(c) Development/design plan
- Development process (including risk assessment)

(d) Documentation
- Documents for users (e.g., mechanism of action of the device, operation and maintenance manual)

(e) Type, structure and validity of safety mechanism/control
- Alarm (e.g., type, display) (Reference: IEC60601-1-8, etc.)
- Emergency stop measures (Reference: ISO10218-1, ISO13850, JIS T2304, etc.)
- Emergency stop device and its structure
- Conditions activating emergency stop (e.g., malfunction against user's intention, time when the safety mechanism is activated)
- State during emergency stop
- Ensuring safety of patients and healthcare professionals during suspension (e.g., holding of device posture)
- Ease of device restart after emergency stop
- Measures to prevent malfunction (user interface)
- Measures to prevent patients or healthcare professionals from falling over or dropping
- Fail-safe
- Fool-proof

(f) Software control robustness

(g) Device specific risk management
- Normal but unexpected operation
- Unexpected movements of humans, animals, and others in environments of use
- Unexpected driving condition (e.g., Mobile robot)
- Uncertainty of object handled (e.g., Mobile servant robot)
- Adaptation to human anatomy and its diversity (e.g., Physical assistant robot)
- Other necessary items

(3) Clinical study (clinical trial) (Reference: PFSB/ELD/OMDE Notification No. 0804001, dated August 4, 2008)

[1] Necessity of clinical trial

If clinical efficacy and safety of the medical device cannot be evaluated only based on results of nonclinical studies such as performance studies or existing literature, etc., clinical studies (clinical trials) will need to be conducted. Submission of data relating to clinical study results will be required.

In addition, if the intended use, performance, structure, etc. are obviously different from those of existing medical devices, data relating to clinical study results will need to be submitted in principle.

[2] Efficacy and Safety Evaluation

Clinical trials should be conducted using devices of which performance, safety, and quality have been adequately confirmed in nonclinical studies.

A clinical trial should be conducted to demonstrate that the investigational device is expected to restore or assist the target motor functions. Thus, in the trial, efficacy and safety of the device should be evaluated according to the protocol formulated with the following items noted. The expected environment of use should also be considered.

(a) Characteristics of devices for restoration of motor functions

1) To demonstrate that a medical intervention technology has efficacy, the trial should include a control group in addition to the intervention group. If a control group cannot be included, information on natural courses after onset of a certain disease should be obtained, and by examining whether clinical courses with the intervention are better than ones expected from the above information, efficacy may be evaluated. A pilot study may also be considered.

2) Motor functions should be assessed by qualitative or quantitative methods for capturing movement patterns and quantitative methods for capturing duration of movement, etc. Quantitative assessment pre- and post-intervention will be useful for indicators of improvement. Rating scales that have been validated for sensitivity, reproducibility, and measuring attributes to a certain extent should be used.

3) To assess upper limb motor functions, simple test for evaluating hand function (STEF), manual function test (MFT), Fugl-Meyer Assessment (FMA), and Wolf Motor Function Test (WMFT) may be used. To assess balance functions, functional reach test (FRT), posturography, timed up and go test (TUG), and Berg Balance Scale (BBS) may be used. To assess walking ability, 10-meter walk speed test, 6-minute walk distance test, and physiological cost index may be used. In addition, surface electromyography and 3-dimensional motion analysis may be used to compare pre- and post-intervention conditions.

4) Changes in activities of daily living (ADL) pre- and post-intervention timepoints should be also taken into account. To assess functions, Barthel Index and function independence measure (FIM) may be used. In addition, to examine whether the intervention improves quality of life (QOL), which is also an important endpoint, EuroQol (EQ-5D), SF-36, visual analog scale (VAS), etc., should be used

(b) Evaluation for reduction of burden on healthcare professionals

Efficacy of a device for restoration of motor functions can be evaluated not only from the viewpoint of investigators who intend to demonstrate usefulness of the device itself but also from the viewpoint of healthcare professionals such as therapists who expect the device to reduce their burden in rehabilitation. Firstly, issues in terms of time such as time taken for attachment should be investigated. In addition, the following points must be clarified: whether the device for restoration of motor functions offers adequate training that healthcare professionals cannot offer on their own; and how the training leads to improvement of movement and activities.

The other important endpoints are how much healthcare professionals' work is reduced by introduction of a device for restoration of motor functions, which should be clearly demonstrated; and to what extent the intervention has improved QOL, which can be assessed using EQ-5D, SF-36, VAS, etc.

[3] Sample size of a clinical trial

Sample size of a clinical study (clinical trial) should be appropriate for efficacy and safety evaluation of the concerned medical device and thus determined in view of the objective of the clinical study and primary endpoint based on scientific evidence. If the clinical study has limitations such as investigational use of an orphan medical device and the limited number of patients eligible for the investigational device, the plan of a clinical trial should be formulated with the evaluable and feasible sample size in view of the limitations.

It should be noted that for a controlled study, the sample size needs to be determined statistically.

Reliable data outside Japan may be attached to the approval application form, but whether the concerned data alone enables clinical evaluation should be adequately examined.

[4] Evaluation period

A clinical trial should be conducted for an appropriate period of time according to the characteristics of subjects. If the product is used over an extended period of time beyond the clinical trial period, implementation of post-marketing surveillance should be considered.

(Attachment 3)

Guidance on Evaluation of Medical Devices for Treatment of Severe Lower Limb Ischemic Diseases

1. Introduction

In patients with arteriosclerosis obliterans, lower extremities have generally favorable prognosis, but once affected by critical limb ischemia, they have poor prognosis and are highly likely to result in leg amputation. The critical limb ischemia has been increasingly prevalent over time with growing populations of the elderly, patients on dialysis, and those with diabetes mellitus, rapidly gaining clinical significance. Because leg amputation not only affects quality of life but also leads to poor prognosis, limb salvage is considered to greatly benefit national medical care and quality of life of the public. In patients with critical limb ischemia, revascularization plays an important role in limb salvage and can be performed by bypass surgery using autologous veins, which is the gold standard procedure. On the other hand, a series of reports have shown that catheterization provides favorable outcomes, and thus intravascular catheterization has been increasingly recognized as a potential alternative to bypass surgery for revascularization. However, this procedure has poor long-term vascular patency and often needs to be repeated in a course up to wound healing. This procedure may prolong wound healing. Medical devices designed to improve vascular patency are expected to improve the lower limb salvage rate and shorten the duration of ulcer healing. Currently, medical devices potentially leading to improved patency are highly needed in clinical settings and thus subject to many currently ongoing research and development projects. If such medical devices with high efficacy are developed, they will benefit not only patients but also medical economics.

Efficacy evaluation of medical devices for treatment of critical limb ischemia has the following problems: (1) critical limb ischemia has poor prognosis both in life and in the lower limbs; (2) vascular lesions are characterized by involvement in multiple vessels and sites; (3) leg ulcers associated with critical limb ischemia as well as wound healing after revascularization are not uniform. These problems complicate efficacy evaluation of medical devices for treatment and thus heavily impair accuracy of the evaluation.

The guidance on evaluation of medical devices for revascularization in lesions affected by critical limb ischemia, which are highly needed in clinical settings, provides requirements for efficacy and safety evaluation as well as points to consider for clinical studies.

2. Scope of the guidance on evaluation

The guidance on evaluation applies to medical devices for revascularization treatment in lesions affected by critical limb ischemia associated with arteriosclerosis obliterans in the lower limb. It does not apply to medical devices for drug therapies for critical limb ischemia or for enhancing wound healing. Medical devices used for therapeutic angiogenesis may be recognized as ones for revascularization in a broad sense but are not included in the scope because they do not directly intervene in arterial blood vessels in the lower limb. However, the guidance on evaluation may guide evaluation of such medical devices in terms of selection of eligible subjects and assessment of wound healing. If having difficulty determining whether the medical device to be developed is subject to the guidance on evaluation, the applicant should consult with the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW.

3. Positioning of the guidance on evaluation

The guidance on evaluation provides matters considered to be important at the present time. It is supposed to be revised in response to further technological innovation and accumulation of knowledge and thus not binding on application data. Evaluation of medical devices subject to the guidance on evaluation requires flexibility based on scientific rationality with full understanding of characteristics of individual products. If a globally clinical trial is conducted in a manner not presented in the guidance on evaluation, the applicant should check whether results from the concerned clinical trial are applicable to clinical practices in Japan, utilizing the Pharmaceutical Affairs Consultation on R&D Strategy or face-to-face consultation of the Pharmaceuticals and Medical Devices Agency at an early stage wherever possible.

4. Assessment of critical limb ischemia

Because patients with critical limb ischemia have widely varied baseline demographics and disease characteristics, patients eligible for evaluation of medical devices used for the treatment should be specified in view of factors determining prognosis of the disease and treatment outcomes. These factors are broadly classified into 3 categories of baseline demographics, vascular characteristics, and wound characteristics.

(1) Baseline demographics

Regardless of success or failure of revascularization, the following patient populations have poor prognosis and thus are not eligible for the clinical trial.

1) Severe heart failure: Cardiac dysfunction can be diagnosed based on left ventricular ejection fraction, BNP or NT pro-BNP values, prior hospitalization due to heart failure, NYHA class, etc. Of note, definition and assessment methods of severe heart failure require consideration.
2) Coexisting severe ischemic heart disease: Because ischemic heart disease is highly likely to coexist and is a factor that determines the prognosis, presence or absence of severe ischemic heart disease should be checked before surgery even in patients without known heart disease if possible.
3) Severe infections: Severe systemic infection signs and severe wound inflammation are both indicative of poor prognosis. For assessment of infection, consideration should be given to CRP cut-off value, etc.
4) Rutherford Class 6: Because major tissue loss needs a long period of time for wound healing and is highly likely to be subject to attempts of all multidisciplinary possible treatments, the lesion of this class is not eligible for evaluation of medical devices for treatment.
5) Heel ulcer: Wound healing is slower than that in other sites, precluding consistent assessment.
6) Multiple ulceration: For multiple ulceration, the upper limit of the size of individual wounds should be determined if possible. Because a larger wound needs a longer period of time for wound healing, such wounds are not eligible for efficacy evaluation based on an extent of wound healing.

7) Oral steroids: Because oral steroids prolong wound healing and are related to susceptibility to infections, patients on oral steroids are not eligible.
8) Low albumin (<3.0 g/dL): The low albumin level is a factor prolonging wound healing, suggesting that the patient has poor baseline demographics.
9) Low BMI (<18): The low BMI level suggests long-term undernutrition and is indicative of poor prognosis.
10) Low ADL: The low ADL score is indicative of poor life prognosis and complicates prediction of treatment outcome.
11) False critical limb ischemia: The lower limb ischemia is not considered responsible for signs representative of critical limb ischemia because blood flow in the lower limb is assessed as adequate by any objective blood flow assessment device.
12) Primary diseases other than arteriosclerosis, such as vasculitis: Because the primary disease is not arteriosclerosis, the lesion is not eligible for efficacy evaluation of medical devices for treatment.

In addition, of the baseline demographics, the following points should be taken into consideration.

1) Age is a factor determining prognosis.
2) For a lesion of Rutherford Class 4, ischemia must be documented by hemodynamic assessment.
3) Dialysis (hemodialysis and peritoneal dialysis) is reported as a factor determining prognosis in both life and lower limb, but patients should not be excluded from a clinical trial only because they are on dialysis for the following consideration: patients on dialysis constitute approximately 50% of patients who received endovascular therapy for critical limb ischemia in Japan and they have better prognosis than those outside Japan. Rather, patients on dialysis free from the above risks should be included in a clinical trial if possible.

(2) Determination of target vessel

Because critical limb ischemia is characterized by involvement in multiple vessels and sites, identification of the responsible lesion is important. In particular, patients with wounds evidently related to the vessel to be treated must be selected in a study of intervention in vascular lesions below the knee. Potentially eligible lesions or patients are as follows.

1) For complex lesions with femoral artery or iliac artery, the lesion in the in-flow artery has been treated precedingly.
2) The lesion has undergone endovascular treatment based on the angiosome concept, either directly or indirectly.
3) After treatment, blood flow toward the wound (wound blush obtainment) has been confirmed
4) For wound-free lesions of Rutherford Class 4, only ones with dilatation of a single vessel should be deemed eligible to simplify interpretation of the relationship between treatment and symptoms.

Use of medical devices for treatment in eligible patients or lesions

1) After confirming that the above criteria are met, the target vessel to use the medical devices for treatment should be determined.
2) Lesions of Rutherford Class 5 may accommodate treatment on multiple vessels, but use of the medical devices for treatment should be limited to the vascular lesion deemed the most important for limb salvage. In addition, the affected limb as a whole should be assessed.
3) Multiple lesions in the same blood vessel should be treated with the same medical device if possible.

(3) Wound assessment

Wounds should be assessed in terms of 5 aspects, size, depth, infection, necrotic tissue, and granulation tissue.

1) Size
   - Using photographs taken with a digital camera, the size should be assessed based on the maximum diameter × the length perpendicular to it.
   - Use of wound area measurement methods (e.g., VISITRAK) may be considered.
2) Depth
   - The depth should be assessed on a 5-category scale: reaching dermis, reaching subcutaneous, reaching muscles and tendons, exposure of bones and joints, and unknown.
3) Infections
   - Using photographs taken with a digital camera, the infection status should be assessed based on findings of redness and swelling. In addition, peripheral blood test (CRP, white blood cell count), plain X-ray for bone destruction, and MRI for signs of osteomyelitis should be performed. MRI should be performed after revascularization to check for signs of osteomyelitis.

5. Efficacy of medical devices for treatment

Efficacy of medical devices for treatment should be evaluated in terms of clinical aspects, vascular lesions, and wound healing.

Lesions of any Rutherford class will be eligible for assessment of vascular lesions, but the lesions of Rutherford Class 4 will not be eligible for assessment of wound healing. Therefore, lesions of Rutherford Classes 4 and 5 cannot be subjected to the efficacy evaluation using the same criteria. Conventional endpoints such as limb salvage rate and amputation-free survival rate count the following patients as limb salvage cases: patients in whom amputation is not performed at the time of assessment although wound healing has not been achieved owing to inadequate reperfusion; and patients who died before leg amputation. Medical devices for reperfusion should be evaluated using vascular patency and wound healing, which potentially reflect the direct effects, as the endpoints. Therefore, clinical evaluation should be conducted in consideration of these points.

(1) Clinical evaluation

Clinical success: It is defined as the condition in which the severity is improved to Rutherford Class 3 or lower, and improved signs are maintained until the designated assessment day. Rutherford Class 4 requires assessment of pain, but no objective assessment methods are currently available. Thus, pain relief accompanied by maintenance of improved blood flow should be assessed. The clinical evaluation described above will be performed at 1, 3, and 6 months.

(2) Vascular lesions

1) Initial response to treatment
   - Extent of residual stenosis on angiography, presence or absence of contrast delay, and presence or absence of vascular complications (vascular perforation, peripheral embolism, and arterial dissection accompanied by delay in blood flow)
   - In-hospital complications within 30 days (e.g., all-cause death, myocardial infarction, stroke, unplanned leg amputation, bleeding complications)

2) Long-term efficacy
   - Presence or absence of leg amputation not planned before revascularization
   - Presence or absence of revascularization based on clinical necessity according to the following criteria
     [1] Revascularization for delayed wound healing with reduced blood flow documented by an objective blood flow assessment device
     [2] Severe stenosis ≥70% on quantitative angiogram or presence of obstruction, with delayed wound healing
   - Time to wound healing (see the Wound healing section)
   - Angiography is the best method for assessment of patency. Therefore, follow-up angiographic assessment is recommended as sub-study. Angiographic assessment should be performed after a 6-month clinical assessment.
   - Although the current evidence is not enough, assessment with an objective blood flow assessment device may be used as an alternative to the patency assessment. The objective blood flow assessment device should be continuously used throughout the course if possible.

(3) Wound healing efficacy

In principle, wound healing should be assessed by an independent third party, and time to the following 2 primary endpoints should be evaluated. Photographs should be taken every 2 weeks for wound assessment.

1) Baseline timepoints

The following 2 timepoints are used as the baseline timepoints for wound healing assessment.

[1] Date of revascularization if no local procedure is required

[2] After debridement and planned minor amputation in patients eligible for local wound surgery

2) Primary endpoints

[1] Epithelialization: It refers to complete epithelialization. That is, it refers to the post-surgery skin condition that has had suture removed, has no exudate, and is intact.

[2] Granulation: Time when the wound is assessed as eligible for closure by skin grafting or cerclage, residual limb surgery, or skin flap procedures should be evaluated. It refers to the condition in which the granulation tissue has matured to 80% or more of the original tissue, no necrotic tissue is observed, and infections are controlled.

3) Other assessment methods for wound healing

The following indices should be assessed at 1, 3, and 6 months after endovascular treatment.

[1] Percent wound area reduction

[2] Final cure rate at the planned level of amputation

6. Safety Evaluation

Safety will be evaluated based on data on adverse events. Perioperative adverse events are roughly classified into those attributable to medical devices for treatment and those related to the procedure.

(1) Adverse events during the specified evaluation period

1) Mortality
2) Leg amputation rate
3) Major cardiovascular events (death, myocardial infarction, stroke, unstable angina, cardiac failure)
4) Major lower limb accidents (unplanned leg amputation or conversion to bypass surgery)

(2) Procedure-related events (occurrence of the event within 30 days after surgery)

1) Perioperative mortality
2) Perioperative major lower limb accidents (unplanned leg amputation or conversion to bypass surgery)
3) Perioperative cardiovascular events (death, myocardial infarction, stroke, unstable angina, cardiac failure)
4) Vascular complications (e.g., perforation, peripheral embolism, dissection accompanied by worsened blood flow, acute vascular occlusion)
5) Puncture site complications (e.g., hematoma requiring transfusion, pseudoaneurysm, arteriovenous fistula)

(3) Events attributable to medical devices for treatment

1) Complications specific to medical devices for treatment
2) Others