October 3, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Platelet-rich plasma gel preparation kit (newly created)
Brand Name	AutoloGel System
Applicant	Rohto Pharmaceutical Co., Ltd.
Date of Application	November 30, 2021 (Application for marketing approval)

Results of Deliberation

In its meeting held on October 3, 2022, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product should be approved without being designated as a medical device subject to a use-results survey. This product should be classified as a biological product.

Review Report

September 7, 2022

Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Platelet-rich plasma gel preparation kit (to be newly created)
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Reviewing Office	Office of Medical Devices II

Review Results

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Results of Review

The AutoloGel System is a preparation kit for autologous platelet-rich plasma (PRP) gel used to promote healing or dressing of wounds that have not responded to conventional treatment. The AutoloGel System consists of a blood collection tube, "Safetouch PSV Set with Luer Adapter" (another company's product already certified in Japan; Certification No. 220AABZX00324000), "Ascorbic Acid Injection 500 mg 'NP'" (another company's product already approved in Japan; Approval No. 22500AMX00817000), "Calcium Chloride Injection 2% 'NP'" (another company's product already approved in Japan; Approval No. 22500AMX00750000), and "Thrombin Oral/Topical 5000 'F'" (another company's product already approved in Japan; Approval No. 21900AMX01684000).

The applicant submitted non-clinical data supporting physicochemical properties, biological safety, stability, durability, performance, and directions for use. The data indicated no particular problems.

The applicant submitted clinical data from a Japanese clinical trial that evaluated the efficacy and safety of wound treatment using the investigational device, which is the development product of the AutoloGel System, in patients with diabetic ulcers that had not responded to conventional treatment. In the Japanese clinical trial, subjects achieving a ≥50% reduction in wound radius in the 8-week treatment period were classified as "responders" and the primary endpoint was "the proportion of responders." The efficacy criterion was ">60% of subjects being responders." In the per-protocol set (PPS) (N = 47), the primary analysis set for efficacy evaluation, 80.9% of subjects were responders, exceeding the efficacy criterion of 60%. In the safety evaluation, no investigational device-related adverse events were reported. The data on the comparable overseas device, "AutoloGel System," obtained from the reported literature did not reveal any device-related adverse events. The above data demonstrated the efficacy and safety of the wound

treatment using the investigational device in patients with diabetic ulcers that had not responded to conventional treatment and were generally considered refractory. This suggests that using the AutoloGel System to promote the healing process of wounds that have not responded to conventional treatment will offer a certain level of clinically meaningful benefit.

To ensure the efficacy and safety of the AutoloGel System, users should be thoroughly familiar with how to use the AutoloGel System. For example, users should know how to select eligible patients and identify wounds suitable for treatment, and should be able to decide when to switch to another treatment in cases where the wound fails to respond to treatment with the AutoloGel System. Therefore, PMDA concluded that the proper use guidelines and other information to be issued by the relevant academic societies should be provided to alert users. PMDA also concluded that no use-results survey is needed in post-marketing settings, because (a) no device-related adverse events were reported in the Japanese clinical trial or in association with the use of the comparable overseas device, and (b) there are no data showing safety concerns associated with the use of PRP centrifuges approved in Japan.

As a result of its review, PMDA has concluded that the AutoloGel System may be approved for the intended use shown below, and that this conclusion should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

The AutoloGel System is used to produce autologous platelet-rich plasma gel for promoting healing of wounds that have not responded to conventional treatment.

Review Report

September 7, 2022

Product for Review

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Term Name	Platelet-rich plasma gel preparation kit (to be newly created)
Brand Name	AutoloGel System
Applicant	Rohto Pharmaceutical Co., Ltd.
Date of Application	November 30, 2021
Proposed Intended Use	The AutoloGel System is intended to be used to produce autologous platelet-rich plasma gel for promoting healing of wounds for which conventional treatment is not indicated.

Table of Contents

List of Abbreviations

ACD-A	Acid Citrate Dextrose-A
CI	Confidence Interval
FAS	Full Analysis Set
bFGF	basic Fibroblast Growth Factor
ISO	International Organization for Standardization
JIS	Japanese Industrial Standard
LOCF	Last Observation Carried Forward
NPWT	Negative Pressure Wound Therapy
PPS	Per Protocol Set
PRP	Platelet Rich Plasma
SD	Standard Deviation
USP	United States Pharmacopeia

I. Product Overview

The AutoloGel System is a preparation kit for autologous platelet-rich plasma (PRP) gel used to promote healing or dressing of wounds that have not responded to conventional treatment. The AutoloGel System has the following constituent parts:

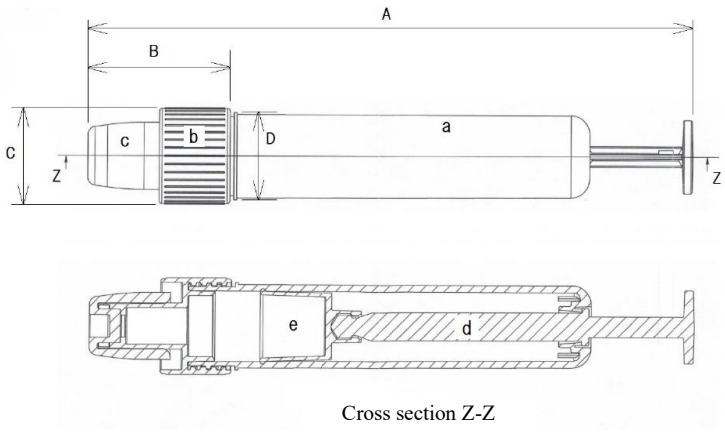
(a) A blood collection tube containing anticoagulant solution A defined in the Minimum Requirements for Biological Products (acid citrate dextrose-A; hereinafter referred to as "ACD-A solution") (Figure 1)

(b) "Safetouch PSV Set with Luer Adapter" (another company's product already certified in Japan, Certification No. 220AABZX00324000) (hereinafter referred to as the "blood collection needle")

(c) "Ascorbic Acid Injection 500 mg 'NP'" (another company's product already approved in Japan; Approval No. 22500AMX00817000) (hereinafter referred to as "ascorbic acid"),

(d) "Calcium Chloride Injection 2% 'NP'" (another company's product already approved in Japan; Approval No. 22500AMX00750000) (hereinafter referred to as "calcium chloride")

(e) "Thrombin Oral/Topical 5000 'F'" (another company's product already approved in Japan; Approval No. 21900AMX01684000) (hereinafter referred to as "thrombin")



Cross section Z-Z

	Name
a	Barrel
b	Plastic cap
c	Rubber cap
d	Plunger
e	Gasket

	Dimension (mm)
A	[redacted]
B	
C	
D	

Figure 1. Appearance of blood collection tube, a constituent part of AutoloGel System

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The following is a summary of data submitted for the present application by the applicant and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA).

The expert advisors present during the Expert Discussion on AutoloGel System declared that they did not fall under the Item 5 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. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

During wound healing, growth factors are involved in the promotion of granulation and epithelialization in the processes of regeneration or remodeling of damaged tissues through tissue reactions, primarily by cell proliferation in the organisms. However, in patients with chronic wounds (e.g., diabetic ulcers, pressure ulcers, venous ulcers) and other certain types of wounds[1], dysfunction of various cells and underlying diseases is considered to cause inflammatory conditions, which reduce production of cell growth factors, resulting in delayed wound healing.[2]

Platelet-rich plasma (PRP) is plasma containing a high concentration of platelets, which can be obtained by centrifugation of blood. Platelets have α-granules (a granular component), which contain platelet-derived growth factor, transforming growth factor β, and other growth factors that accelerate wound healing.[3] PRP is not suitable for wounds caused by malignant tumors or wounds with active infections because growth factors may exacerbate symptoms. PRP is expected to be effective in the treatment of chronic wounds.

Medical devices for the preparation of PRP include the "GPS III System," a device from another company already approved in Japan (Approval No. 22700BZX00420000). The GPS III System is used to prepare PRP liquid by centrifugation.[4] The AutoloGel System is also used to prepare a PRP liquid by centrifugation, but then the liquid is transferred to a sterilized petri dish. The PRP liquid in the petri dish is mixed with agents to produce a fibrin matrix and thereby converted into a gel. The PRP gel easily stays in place over the wound bed because it has higher viscosity than PRP liquid. Because of its dressing effect, the PRP gel is expected to more easily (a) maintain a

moist wound bed environment and (b) allow the wound tissue to come in contact with growth factors such as platelet-derived growth factor, compared with PRP liquid.

1.A.(2) Use in foreign countries

Products exactly the same as this AutoloGel System have not been licensed outside Japan. In the US, Cytomedix started marketing the "*AutoloGel System*" in 2007 (hereinafter referred to as the "comparable overseas device"), which was subsequently marketed as the "Aurix System" by Nuo Therapeutics, Inc. In 2019, its sales were discontinued when Nuo Therapeutics, Inc. ceased to operate (Table 1). The comparable overseas device includes a centrifuge as a constituent part, while the AutoloGel System does not. However, both devices are conceptually similar in that they are used to produce PRP gel to promote wound healing.

Table 1. Licensing of the comparable overseas device

Country	Brand name (510k number)	Approval date	Intended use or indication	Remark
US	AutoloGel System (BK060007)	2007	The AutoloGel™ System is intended to be used at point-of-care for the safe and rapid preparation of platelet-rich plasma (PRP) gel from a small sample of a patient's own blood. Under the supervision of a healthcare professional, the PRP gel produced by the AutoloGel™ System is suitable for exuding wounds, such as leg ulcers, pressure ulcers, and diabetic ulcers and for the management of mechanically or surgically-debrided wounds.	Brand name was changed to "Aurix System" in 2014.

1.A.(3) Malfunctions and adverse events in foreign countries

To identify the types and scale of malfunctions that may occur in association with the AutoloGel System, the applicant submitted a report on malfunctions and adverse events that had occurred with the comparable overseas device between 2010 and 2016 (the applicant was able to collect data during this period). The data showed no serious malfunctions requiring discontinuation of wound treatment and no adverse events associated with the comparable overseas device (Table 2).

Table 2. Malfunctions that occurred with the comparable overseas device*

Constituent parts	Malfunction	2010	2011	2012	2013	2014	2015	2016	Total
Blood collection tube	Insufficient blood collection	0	1	0	3	1	0	0	5
	Missing parts	0	1	2	0	0	1	0	4
	Abnormal gelling time	0	0	0	0	0	2	0	2
	Lid broken	0	1	0	0	0	0	0	1
Centrifuge**	Abnormal power code	0	2	0	3	1	1	1	8
	No power	0	0	2	0	1	4	0	7
	Abnormal lid latch parts	0	1	0	4	1	1	0	7
	Abnormal rotation speed	0	2	2	0	1	0	1	6
	Unknown alarm	0	0	1	0	1	0	0	2
	Tilted rotor axis	0	0	0	0	0	1	0	1
	Abnormal vibration	1	0	0	0	0	0	0	1
Total		1	8	7	10	6	10	2	44

* The applicant analyzed the data for the period between 2010 and 2016 only because Nuo Therapeutics, Inc. ceased to operate.
** The AutoloGel System does not contain a centrifuge as a constituent part.

2. Design and Development

2.(1) Physicochemical properties

2.(1).A Summary of the data submitted

The applicant submitted data on the testing of draw volume of blood collection tubes, leakage from container, robustness of container, and extractables from container as data relating to physicochemical properties. When drawing blood using the AutoloGel System, the blood collection tube is evacuated by the user to create a vacuum inside (a condition in which the air pressure is below the prevailing atmospheric pressure[5]). Therefore the AutoloGel System was tested in accordance with JIS T 3233:2011[6] or JIS T 3211:2011,[7] and the results of all tests met the conformity criteria. Based on the above test results, the proposed performance and safety specifications for the AutoloGel System included the draw volume of the blood collection tube, leakage from the container, and robustness of the container. The applicant considered that a specification for extractables from the container was unnecessary because the biological safety specifications were already prepared.

2.(1).B Outline of the review conducted by PMDA

The AutoloGel System needs to have sufficient durability against various loads resulting from drawing blood, mixing chemical agents and centrifugation; in addition, the AutoloGel System needs to have a blood holding container suitable in terms of extractables. The submitted data showed that the blood collection tube was sufficiently durable for PRP gel preparation, and that no extractables of concern were detected from the tube as a blood holding container. PMDA reviewed the appropriateness of specifications, applicable standards, testing methods and results

based on data discussed later in Section "2.(7) Performance" and the results of a general clinical study in patients with diabetic ulcers (hereinafter referred to as the "Japanese clinical trial"), in which PRP gel was successfully prepared (see Section "6. Clinical data or alternative data accepted by the Minister of Health, Labour and Welfare."). PMDA considered that there were no particular problems.

2.(2) Electrical safety and electromagnetic compatibility

2.(2).A Summary of the data submitted

Data on electrical safety and electromagnetic compatibility were not submitted because the AutoloGel System does not use electricity.

2.(2).B Outline of the review conducted by PMDA

PMDA concluded that it is reasonable not to submit data on electrical safety and electromagnetic compatibility.

2.(3) Biological safety

2.(3).A Summary of the data submitted

To support biological safety, the applicant submitted the data from the testing of the blood collection tube (cytotoxicity), intradermal sensitization, acute systemic toxicity, pyrogen, and blood compatibility. The ACD-A solution to be contained in blood collection tubes conforms to [redacted], and information in the safety data sheet clearly indicates that biological safety is ensured. Therefore, a biological safety evaluation was not performed.

2.(3).B Outline of the review conducted by PMDA

PMDA's view:

Since the PRP gel prepared with the AutoloGel System comes in contact with the wound surface, the prepared PRP gel should be subject to biological safety evaluation. PMDA asked the applicant to explain this issue.

The applicant's response:

The biological safety of PRP gel has been ensured based on the following data:

(a) Mixing of chemical agents included as constituent parts does not produce any new substance of safety concern.

(b) No local irritation resulting from PRP gel application was reported in studies summarized in Section "2.(7) Performance" or in the Japanese clinical trial (see Section "6. Clinical

data or alternative data accepted by the Minister of Health, Labour and Welfare.")

Based on the above, PMDA reviewed the submitted data from various studies, and concluded that there were no particular problems with the biological safety of the AutoloGel System.

2.(4) Radiation safety

2.(4).A Summary of the data submitted

Data on radiation safety were not submitted because the AutoloGel System does not emit radiation.

2.(4).B Outline of the review conducted by PMDA

PMDA concluded that it is reasonable not to submit data on radiation safety.

2.(5) Mechanical safety

2.(5).A Summary of the data submitted

Data on mechanical safety were not submitted because the AutoloGel System is not a device requiring mechanical safety in clinical use.

2.(5).B Outline of the review conducted by PMDA

PMDA concluded that it is reasonable not to submit data on mechanical safety.

2.(6) Stability and durability

2.(6).A Summary of the data submitted

The applicant submitted data on the testing of draw volume of electron-beam sterilized blood collection tubes stored [redacted] at [redacted]°C, leakage from container, robustness of container, and extractables from container, and [redacted] the ACD-A solution stored [redacted] at [redacted]°C and [redacted]%RH humidity. The data demonstrated that the blood collection tube and ACD-A solution can be stored for up to 1.5 years at room temperature after electron-beam sterilization. No stability or durability evaluation was performed on the blood collection needle, ascorbic acid, calcium chloride, or thrombin because they were to meet the respective requirements specified in the marketing certification or marketing approval of the certified/approved products of other companies. The proposed storage environment/duration at room temperature was 2.5 years for the chemical agents stored at 1°C to 10°C and 1.5 years for the blood collection needle.

2.(6).B Outline of the review conducted by PMDA

PMDA reviewed the data on the stability and durability of the AutoloGel System and concluded that there was no particular problem.

2.(7) Performance

2.(7).A Summary of the data submitted

The applicant submitted data from a platelet concentration study and a study to support the mechanism of action of PRP gel for the evaluation of performance of the AutoloGel System.

2.(7).A.1) Platelet concentration study

The platelet concentration ratio, red blood cell removal rate, and white blood cell removal rate of PRP produced by the AutoloGel System were evaluated. The results demonstrated that under the prespecified centrifugation conditions (centrifugal force of 4236 × *g*; centrifugal cycle, 30 seconds), the AutoloGel System can prepare PRP with a platelet concentration that can be used for wound healing.

Using the blood collection needle and a syringe, approximately 6 mL of blood was collected from each of the healthy donors aged [redacted] years to [redacted] years (N = [redacted]). The blood was drawn into a blood collection tube containing ACD-A solution and then centrifuged under the prespecified conditions to create PRP fractions. The platelet concentration ratio, red blood cell removal rate, and white blood cell removal rate of PRP were evaluated by comparing the mean platelet, red blood cell, and white blood cell counts (per 1 μL) in the PRP fraction with those in whole blood. The platelet concentration ratio was [redacted]%, red blood cell removal rate was [redacted]%, and white blood cell removal rate was [redacted]% (Table 3).

Table 3. Results of platelet concentration ratio, red blood cell removal rate, and white blood cell removal rate

	Whole blood (/μL)	PRP (/μL)	Concentration ratio (%)	Removal rate (%)
Platelet	[redacted]	[redacted]	[redacted]	
Red blood cell				[redacted]
White blood cell				[redacted]

2.(7).A.2) Study to support the mechanism of action of PRP gel

The wound healing process was evaluated in a rat skin defect model (N = [redacted]; body weight, [redacted]g; [redacted] weeks of age at the time of gel application). The evaluation of wound area and the results of a histopathological examination suggested that PRP gel prepared with the

AutoloGel System contributed to wound healing.

On the day the rat skin defect model was created (Day 0), [redacted] in [redacted] animals in the PRP group and [redacted] animals in the untreated group (control group) [redacted] μL/body of PRP gel, which was prepared with blood from [redacted] ([redacted] weeks of age at the time of blood collection) was applied to each model animal in the PRP gel group. Wound area was measured in [redacted] animals in each group [redacted] days later (Day[redacted]), and in [redacted] animals in each group [redacted] days later (Day[redacted]). A skin histopathological examination was performed in [redacted] animals in each group on Days [redacted] and [redacted] to evaluate healing status of the skin. The wound area [redacted] histopathological evaluation [redacted].

The Student's t-test did not show significant differences in wound area on Day [redacted] between the PRP group and the control group, but the estimated mean wound area at each time point tended to be smaller in the PRP group than in the control group (Table 4).

Table 4. Comparison of wound area between the PRP group and control group

	Wound area [mean ± SD] (mm^2)		
	Day [redacted] (N = [redacted])	Day [redacted] (N = [redacted])	Day [redacted] (N = [redacted])
PRP gel	[redacted]		
Control			

In the histopathological evaluation, [redacted] on Day [redacted], [redacted] on Day [redacted] (Table 5; definitions of wound scores are provided in the table). On Day [redacted], [redacted] in the PRP gel group and [redacted] in the control group. [redacted] in the PRP gel group and [redacted] in the control group. On Day [redacted], [redacted] in the PRP gel and control groups. [redacted] in the PRP gel and control groups. Significant [redacted] in the PRP gel and control groups.

Table 5. Results of histopathological examination

	Wound score*	Day [redacted]		Day [redacted]	
		PRP (N = [redacted])	Control (N = [redacted])	PRP (N = [redacted])	Control (N = [redacted])
[redacted]					

* The definitions of each wound score are as follows.

[redacted]

2.(7).B Outline of the review conducted by PMDA

PMDA reviewed the performance data and concluded that there was no particular problem (see below).

PMDA's view:

1) The mean platelet concentration ratio of PRP prepared by the AutoloGel System was [redacted]% in the study of separation of PRP and concentration of platelets, as discussed earlier in Section 2.(7).A.1). PMDA therefore considered that the AutoloGel System, if used under the prespecified centrifugation conditions, can prepare PRP with a platelet concentration higher than that of whole blood. However, since there are individual differences in platelet counts and in the volume of PRP that can be prepared, it is difficult to specify a specific platelet concentration ratio in the approval document as the specification for the AutoloGel System. Meanwhile, the concentration ratio is expressed as a multiple (fold) in the approval document for another company's PRP preparation device already approved in Japan. Therefore, based on the platelet concentration ratio obtained in the study of separation of PRP and concentration of platelets, the "Performance and Safety Specifications" section of the application document should specify "[redacted]-fold" as the platelet concentration ratio for the AutoloGel System.

2) The wound area of the PRP gel group did not differ significantly from that of the control group, as discussed earlier in Section 2.(7).A.2), but the estimated mean wound area at each time point were smaller in the PRP group than in the control group and the results of histopathological evaluation did not deny wound treatment with the AutoloGel System. PMDA thus concluded that PRP gel prepared with the AutoloGel System will contribute to wound healing.

2.(8) Directions for use

2.(8).A Summary of the data submitted

Data supporting the directions for use of the AutoloGel System were not submitted because multiple medical devices for separation of PRP have been approved in Japan, and preparation of PRP by centrifugation does not involve a special operation. The mixing ratios of constituent chemicals were selected based on data described earlier in Section "2.(7) Performance" and data from the Japanese clinical trial described later in Section "6. Clinical data or alternative data accepted by the Minister of Health, Labour and Welfare" (Table 6).

Table 6. Mixing ratios of PRP and chemical agents (approximate)

PRP (mL)	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Ascorbic acid (mL)	0.3	0.3	0.4	0.4	0.5	0.6	0.6
Thrombin with calcium chloride (mL)	0.3	0.3	0.4	0.4	0.5	0.6	0.6
PRP gel volume (mL)	2.6	3.1	3.8	4.3	5.0	5.7	6.2

2.(8).B Outline of the review conducted by PMDA

PMDA's view:

Since the AutoloGel System is a treatment involving removal of the patient's blood, the following requirements should be satisfied:

(a) The AutoloGel System should not be used to treat wounds of a size (area) that have not been shown to respond to treatment with the AutoloGel System.
(b) Platelets can be concentrated under the specified centrifugation conditions.
(c) The amount of thrombin to be used should be safe for humans.
(d) Wound dressing should be performed in a consistent way.

PMDA asked the applicant to explain 1) approximate wound area allowed for treatment; 2) how to calculate wound area; 3) centrifugation conditions; 4) the amount of thrombin to be used; and 5) how to apply PRP gel and how to protect the wound after application.

The applicant's response:

2.(8).B.1) Approximate wound area allowed for treatment

As described later in Section "6. Clinical data or alternative data accepted by the Minister of Health, Labour and Welfare," wounds of ≤25 cm^2 were allowed for treatment in the Japanese clinical trial. However, wounds of ≥25 cm^2 have been treated with the comparable overseas device according to its data.[8,9,10,11] Therefore wounds of up to roughly 50 cm^2 will be allowed for treatment with the AutoloGel System.

2.(8).B.2) How to calculate wound area

Based on the Japanese clinical trial described later in Section "6. Clinical data or alternative data accepted by the Minister of Health, Labour and Welfare," the wound bed area should be calculated as the product of "the greatest length" and "the width" of the wound bed. "Wound bed" is defined as the surface area of damaged skin, "greatest length" as the maximum length from end-to-end of the wound bed, and the "width" as the maximum dimension perpendicular to the greatest length.

2.(8).B.3) Centrifugation conditions

Platelets were successfully concentrated in the study on the separation of PRP and concentration of platelets as discussed earlier in Section 2.(7).A.1); therefore, centrifugal force of 4236 × *g* and centrifugal cycle of 30 seconds were selected as the centrifugation conditions.

2.(8).B.4) Amount of thrombin to be used

The thrombin concentration in PRP gel is 100 units/mL, and the amount of thrombin contained in the volume of PRP gel to be prepared for the maximum wound area (roughly 25 cm^2) is approximately 6.25 mL, which would contain 625 units of thrombin. This is within the range of the pharmaceutical dosage regimen for thrombin (thrombin reconstituted with physiological saline at a concentration of 50 to 1000 units/mL is sprayed topically over the bleeding site); therefore, the amount of thrombin is safe for human use.

2.(8).B.5) How to apply PRP gel and how to protect the wound after application

Based on the Japanese clinical trial described later in Section "6. Clinical data or alternative data accepted by the Minister of Health, Labour and Welfare," the following methods of PRP gel application and wound protection after application will be used:

- PRP gel should be applied uniformly over the wound surface, and covered with a primary dressing using non-absorbable dressing material, etc. Absorbable dressing materials should not be used as they absorb PRP.

- A secondary dressing should be applied to contain exudates.
- The wound should be coated with PRP gel for ≥24 hours. After 24 hours, if the wound bed has to be cleaned due to leakage of large amounts of exudates, necrotic tissue adhered onto the wound surface, and other reasons, PRP gel should be removed and wound dressing materials should be changed.

The applicant also explained that it would include the above matters in the "Shape, structure, and principles" section or "Usage" section of the medical device application data to ensure that the AutoloGel System is used properly.

PMDA asked the applicant to reconsider the proposed wound area allowed for treatment with the AutoloGel System because the Japanese clinical trial evaluated the efficacy using wounds of ≤25 cm^2. The applicant responded that the maximum wound area allowed for treatment with AutoloGel System will be changed to roughly 25 cm^2.

PMDA's view:

Given the individual differences in wound area and the volume of PRP gel that can be prepared, it is reasonable to specify an approximate wound area (i.e., roughly ≤25 cm^2) that can be treated with the AutoloGel System in the approval document. The amount of thrombin to be used with the AutoloGel System is within the pharmaceutical dosage regimen of thrombin; this means that the safety of thrombin in human use is ensured. PMDA also reviewed the evaluation of the other issues related to directions for use, and concluded that there was no particular problem.

2.(9) Performance and safety specifications

2.(9).A Summary of the data submitted

The proposed performance and safety specifications included the platelet concentration ratio, draw volume of the blood collection tube, leakage and robustness of the container, and biological safety. The applicant submitted data justifying the proposed specifications.

2.(9).B Outline of the review conducted by PMDA

PMDA considered the platelet concentration ratio should be included in specifications and requested that the applicant take actions accordingly. The applicant responded that the platelet concentration ratio is added to the performance and safety specifications. PMDA reviewed data regarding Sections "2.(1) Physicochemical properties," "2.(3) Biological safety," "2.(6) Stability and durability," "2.(7) Performance" and "2.(8) Directions for use" as described earlier, and concluded that there were no particular problems with the specifications of the AutoloGel System.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the AutoloGel System meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHLW Public Notice No. 122, 2005; hereinafter referred to as "the Essential Principles").

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the AutoloGel System to the Essential Principles.

(1) The conformity of the AutoloGel System to Article 3, which stipulates the performance and function of medical devices

PMDA's view:

As described earlier in Section "2.(7).B Outline of the review conducted by PMDA," PRP prepared by the AutoloGel System was evaluated and shown to have a platelet concentration ratio of [redacted]%, indicating that the AutoloGel System can prepare PRP with a platelet concentration higher than that of whole blood. Based on this evaluation result, it is reasonable to specify the platelet concentration capacity of the AutoloGel System as [redacted]-fold increase in platelet concentration.

(2) The conformity of the AutoloGel System to Article 4, which stipulates the term of validity or lifetime of medical devices, and to Article 5, which stipulates the transport and storage, etc. of the medical devices

PMDA's view:

As described earlier in Section "2.(6).B Outline of the review conducted by PMDA," PMDA reviewed the evaluation of the blood collection tube and other components, and concluded that the efficacy and safety of the PRP gel to be prepared are ensured after going through production processes.

(3) The conformity of the AutoloGel System to Article 6, which stipulates the efficacy of medical

devices

PMDA's view:

As discussed later in Section "6.B Outline of the review conducted by PMDA," the submitted study results showed that the AutoloGel System offers a certain clinically meaningful benefit in the treatment of diabetic ulcers not responding to protocol-specified conventional treatment. Since diabetic ulcers are more refractory than other wounds, it is acceptable not to limit the indication of the AutoloGel System to diabetic ulcers. As discussed in Section "6.B Outline of the review conducted by PMDA," the indication of the AutoloGel System should be changed from "wounds for which conventional treatment is not indicated" to "wounds that have not responded to conventional treatment."

(4) The conformity of the AutoloGel System to Article 7, which stipulates the biological safety and other aspects of medical devices

PMDA's view:

The biological safety of the AutoloGel System is ensured for the following reasons:

- As discussed earlier in Section "2.(3).B Outline of the review conducted by PMDA," the biological safety of PRP gel was evaluated because PRP gel is to come in contact with the wound bed. The results indicated that no substances of safety concern would be generated by mixing of the agents.
- Local irritation associated with PRP gel application was not observed in the Japanese clinical trial described later in Section "6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare."

(5) The conformity of the AutoloGel System to Article 8, which stipulates the prevention of microbial contamination by medical devices incorporating tissue of animal origin, etc.

PMDA's view:

As discussed later in Section "5.B Outline of the review conducted by PMDA," the AutoloGel System meets the requirements of General Rule 1-10 of the Standards for Biological Ingredients (MHLW Public Notice No.37, 2018), indicating that the safety of the AutoloGel System containing ingredients of animal origin is ensured.

(6) The conformity of the AutoloGel System to Article 17, which stipulates general requirements for information provision to users (i.e., publicizing precautions and specifying such information in the package inserts) (hereinafter referred to as "Information on Precautions, etc.")

PMDA's view:

As discussed later in Section "6.B.(4) Post-marketing safety measures," the method of proper use should be made widely known to healthcare professionals in the medical fields in which the AutoloGel System is expected to be used for wound treatment; therefore, the applicant should release proper use guidelines in cooperation with relevant academic societies. The applicant should add a statement in the "WARNINGS" section of the package insert to the effect that the proper use guidelines established by the relevant academic societies should be followed when using the AutoloGel System.

Based on the above, PMDA comprehensively reviewed the conformity of the AutoloGel System to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted documents showing a summary of risk management, the risk management system, and its implementation status in accordance with ISO 14971: 2007.[12]

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the risk management documents, taking into account the issues discussed in Section "3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices," and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the manufacturing process and manufacturing site of the AutoloGel System, and data on in-process tests to be performed for evaluation of quality control. The applicant explained that thrombin is included as a constituent part without being processed and was shown to meet the requirements of General Rule 1-10 of the Standards for Biological Ingredients (MHLW Public Notice No.37, 2018).

5.B Outline of the review conducted by PMDA

PMDA examined the submitted data, and concluded that the safety of the following parts were ensured: (a) the blood collection tube, (b) blood collection needle, and (c) gelling agents to prepare PRP gel from PRP liquid. Further, thrombin is included as a component without being processed,

and as discussed earlier in Section "2.(8).B.4) Amount of thrombin to be used," the amount of thrombin to be used with the AutoloGel System is within the range of the pharmaceutical dosage regimen for thrombin and is therefore safe in human use. Therefore, PMDA concluded that the AutoloGel System meets the requirements of General Rule 1-10 of the Standards for Biological Ingredients (MHLW Public Notice No.37, 2018).

Based on the above, PMDA reviewed the data relating to the manufacturing process, and concluded that there was no particular problem.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

For the evaluation of clinical study data, the applicant submitted the results from the Japanese clinical trial. The applicant also submitted a report on the clinical use of the comparable overseas device as reference data.

6.A Summary of the data submitted

6.A.(1) Japanese clinical trial

A Japanese clinical trial was conducted to evaluate the usefulness of wound treatment using the investigational device, which had constituent parts different from those of the AutoloGel System, in patients with diabetic ulcers that had not responded to conventional treatment (Table 7). Because the intended use of the AutoloGel System is treatment of wounds that have not responded to conventional treatment, the Japanese clinical trial was not designed to test the superiority or non-inferiority of the AutoloGel System to conventional treatment as the control.

Table 7. Outline of Japanese clinical trial

<table>
<tr><td>Study title</td><td>General clinical study in patients with diabetic ulcers</td></tr>
<tr><td>Study type</td><td>Open-label, uncontrolled, multicenter</td></tr>
<tr><td>Number of sites</td><td>15 study centers</td></tr>
<tr><td>Study period</td><td>From [redacted], to [redacted], 20[redacted]</td></tr>
<tr><td>Study population</td><td><u>Diabetic ulcers that have not responded to conventional treatment (no trend towards reduction in wound area after ≥4 weeks of conventional treatment)</u>
Definition of conventional treatment
<table>
<tr><td>Pharmaceutical product</td><td>Trafermin (genetical recombination), alprostadil alfadex, bucladesine sodium, deproteinized calf blood extract, tretinoin tocoferil, sucrose and povidone-iodine, lysozyme hydrochloride, iodine, dimethyl isopropylazulene, zinc oxide, cadexomer iodine, sulfadiazine silver, dextranomer, bromelain, povidone-iodine, iodoform, fradiomycin sulfate and trypsin crystallized, alcloxa</td></tr>
<tr><td>Wound dressing material</td><td>Polyurethane film, hydrocolloid, hydrogel, polyurethane foam, hydrophilic fiber, hydrophilic membrane, hydrophilic foam, polymer, non-adherent coating gauze dressing</td></tr>
</table>
Negative-pressure wound therapy (NPWT) is not included in conventional treatment. The presence/absence of prior NPWT will not affect eligibility.

Definition of “no trend towards reduction in wound area”
A status that meets one of the following conditions
➢ Conventional treatment does not result in a change in wound area.
➢ Although the wound area is reduced at the beginning phase of conventional treatment, thereafter, the wound does not show adequate reduction, and wounds requiring treatment are still present.

Size of wound
<table>
<tr><td>Area (area is calculated by multiplying the greatest length by the width)</td><td>≥1 cm^2 and ≤25 cm^2</td></tr>
<tr><td>Depth</td><td>Minimum 0.2 cm, maximum 1.5 cm</td></tr>
</table>
Analysis sets Full analysis set (FAS) and safety analysis set, N = 54; PPS, N = 47</td></tr>
<tr><td>Screening period, treatment period, and frequency of visits</td><td>Screening period
Treat diabetic ulcers with at least 1 conventional therapy (Table 8) for ≥4 weeks and confirm that there is no trend towards reduction in wound area. A screening period is not required if medical records indicate that diabetic ulcers that were treated with conventional therapies for ≥4 weeks show no trend towards reduction in wound area.

Treatment period
The wound is treated with the investigational device for 8 weeks. The use of the investigational device is discontinued if treatment becomes unnecessary by the 8-week visit due to epithelialization or other reasons. Patients are prohibited from concomitantly using the following treatments, but are allowed to continue to use other conservative treatments:
1) Hyperbaric oxygen therapy
2) Hyperthermia treatment
3) LDL-apheresis
4) NPWT to the target wound site
5) Enzymatic debridement of the target wound site
6) Surgical debridement of the target wound site, which involves tissue removal (radical debridement performed in an operating room)
7) Application of topical antiulcer agents and wound dressings to the target wound site
8) Maggot therapy of the target wound site
9) Treatment with other investigational devices, etc. (including clinical trials of pharmaceutical drugs and regenerative medical products)
10) Systemic immunosuppressants
11) Systemic corticosteroids
12) Procoagulants (hemocoagulase), antiplasmin (tranexamic acid), aprotinin
13) Other treatments for the purpose of wound treatment of the target site</td></tr>
</table>

	Frequency of visits After registration, twice a week. At each visit, blood is sampled to prepare PRP gel, which is applied to the target site (applied up to 16 times in the 8-week study period). The following are measured: wound radius, wound area, wound volume, greatest length of wound, wound score, and judgement as to whether the wound can be closed by secondary healing or by relatively simple surgical techniques (e.g., skin grafting, suturing).
Method of use of PRP gel	Prepared PRP gel is applied to the wound for ≥24 hours. After ≥24 hours of PRP gel application, conservative treatment is performed until the next application of PRP gel.
Investigational device	The investigational device consists of a centrifuge, blood collection kit, and gelling agents to prepare PRP gel from PRP liquid (Table 9). The investigational device and the AutoloGel System have different constituent parts (the AutoloGel System does not have a centrifuge and has a different blood collection kit), but are equivalent in PRP gel preparation.
Primary endpoint	**Proportion of responders (i.e., subjects who achieved a ≥50% reduction in wound radius at the final evaluation)** $\text{Wound radius (cm)} = \frac{\text{Target wound area}}{\text{Wound perimeter of target site}} \times 2$ $\text{Wound radius reduction rate (\%)} = \frac{(\text{wound radius at the start of treatment} - \text{wound radius at the final evaluation})}{\text{wound radius at the start of treatment}} \times 100$ **Area and perimeter of wound site** Physician [redacted] measured the area of the wound site and the wound perimeter. **Efficacy criterion** ≥60% of subjects being responders **Analysis set** PPS (N = 47) **Results** In total, 38 of the 47 subjects in the PPS achieved a ≥50% reduction in wound radius. The proportion of responders was 80.9% (95% CI: 66.7, 90.9), which exceeded the efficacy criterion.
Secondary endpoints	**Efficacy** (1) Wound area and reduction (%) in wound area at the final evaluation (last observation carried forward [LOCF]) (2) Wound volume and reduction (%) in wound volume at the final evaluation (LOCF) (3) Time course change in the greatest length of wound (LOCF) (4) Time course change in wound score (investigator's assessment and the independent review committee's assessment*) (LOCF) (5) Time to judgement that wound closure is possible by secondary healing or by relatively simple surgical techniques (investigator's assessment and the independent review committee's assessment*) * The above secondary efficacy endpoints (4) (5) are assessed by independent review committee members based on digital images. The committee members are ulcer treatment specialists who have not been involved in treatment or evaluation of subjects in the Japanese clinical trial. The Japanese clinical trial did not require digital images to be taken by the same physician. Digital cameras and photographing manuals were provided to medical institutions to standardize the imaging conditions and processes. **Safety** Incidences of adverse events and malfunctions **Results overview** For all secondary endpoints, the results supported the effectiveness of wound treatment with the investigational device, and no investigational device-related adverse events were reported.

Table 8. Number of subjects and their prior conventional treatment*

		PPS (number of subjects)	FAS (number of subjects
Pharmaceutical product	Sucrose and povidone-iodine	20	22
	Trafermin (genetical recombination)	17	18
	Alprostadil alfadex	9	12
	Bucladesine sodium	2	2
	Iodine	10	11
	Lysozyme hydrochloride	4	5
	Iodoform	4	4
	Sulfadiazine silver	3	3
Wound dressing material	Non-adherent coating gauze	6	7
	Polyurethane foam	6	7
	Povidone-iodine	6	6
	Hydrophilic fiber	3	4

* Some subjects had received more than one type of treatment, and the sum total of the categories is greater than the total number of subjects.

Table 9. Comparison of the investigational device and the AutoloGel System

	Investigational device	AutoloGel System
Centrifuge	Bench-top centrifuge ([redacted])	(Not included)
Blood collection kit	[redacted] ([redacted]) The blood collection tube contains [redacted] mL of ACD-A solution.	Blood collection tube (6.0 mL) The blood collection tube contains [redacted] mL of ACD-A solution.
	[redacted] ([redacted])	Safetouch PSV Set with Luer Adapter
Chemical agents	Ascorbic Acid Injection 500 mg “NP”	
	Calcium Chloride Injection 2% “NP”	
	Thrombin Oral/Topical 5000 “F”	

6.A.(1).1) Patient characteristics

6.A.(1).1).(a) Disposition of subjects

The disposition of subjects in the general clinical study of the investigational device in patients with diabetic ulcers is shown below. In the Japanese clinical study, informed consent was obtained from 74 subjects (Figure 2). In total, 54 subjects enrolled in the Japanese clinical trial received treatment, and 26 subjects completed the 8-week treatment period. A total of 28 subjects discontinued the study because “treatment became no longer necessary by the 8-week visit due to epithelialization or other reasons” (25 subjects), “the (sub)investigator decided to withdraw the subject because of adverse events” (2 subjects), and “the subject was found not to meet the inclusion criteria or found to meet the exclusion criteria” (1 subject). In all subjects, diabetic ulcers were situated in the lower extremities.

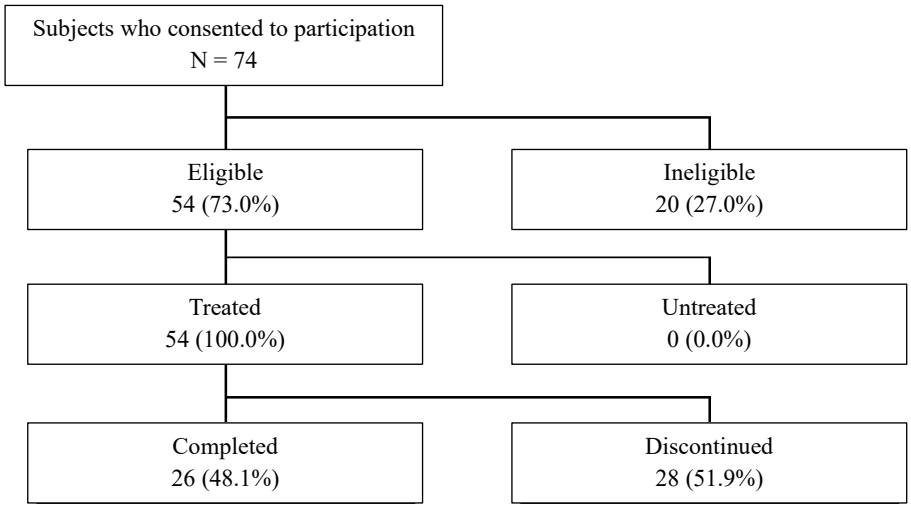


Figure 2. Disposition of subjects

6.A.(1).1).(b) Status of PRP gel applied

To evaluate the status of PRP gel treatment in the Japanese clinical trial, the number of blood collection tubes used for PRP gel preparation, and the number of PRP applications performed were recorded (Table 10).

Table 10. The number of blood collection tubes used for PRP gel preparation and the number of PRP applications

	PPS			FAS		
	Mean ± SD	Min	Max	Mean ± SD	Min	Max
No. of blood collection tubes used	12.3 ± 5.05	3	22	12.0 ± 5.05	3	22
No. of PRP applications	12.0 ± 4.77	3	16	11.6 ± 4.85	3	16
No. of PRP applications administered / No. of PRP applications planned by the (sub)investigator (%)	99.9 ± 0.91	93.8	100	99.9 ± 0.85	93.8	100

6.A.(1).1).(c) Analysis sets

In the Japanese clinical trial, the FAS, PPS, and the safety analysis set were defined (Table 11), and the PPS was the primary analysis set in the efficacy evaluation. The FAS and the safety analysis set included 54 subjects while the PPS included 47 subjects.

Table 11. Summary of analysis sets

	Definition
FAS	An analysis set that consists of all enrolled patients excluding those who meet any of the following ➢ Patients who do not have diabetic ulcers ➢ Patients who have not received PRP gel ➢ Patients who have no evaluable efficacy data after receiving PRP gel ➢ Patients who have not consented to participation
PPS	An analysis set that consists of FAS patients excluding those who meet any of the following ➢ Patients who were found not to have met the inclusion criteria after enrollment ➢ Patients who were found to have met the exclusion criteria after enrollment ➢ Patients who have received prohibited concomitant treatment ➢ Patients whose number of PRP gel applications is <75% of the number of PRP applications planned by the (sub)investigator ➢ Patients whose wound radius at the start of treatment cannot be calculated
Safety analysis set	An analysis set of patients who received at least one PRP gel application

6.A.(1).2) Results of the primary endpoint

The primary endpoint in the Japanese clinical trial was the proportion of responders (i.e., subjects who achieved a ≥50% reduction in wound radius at the final evaluation). The wound area/wound perimeter ($\pi r^2/2\pi r$ = r/2 in a circular wound) is an indicator[13] to assess the distance of wound edge migration[14] over time. Wound radius (r), which is obtained by multiplying r/2 by 2, was used as the indicator because it is not affected by the shape of wound surface. The wound radius reduction rate was measured every 3 days. In the clinical studies of the ointment containing sucrose and povidone-iodine and trafermin (genetical recombination) (hereinafter referred to as "trafermin"), drugs which are used for treatment of skin ulcers in Japan, a ≥50% reduction in wound area was used as the clinical indicator.[15,16] A 50% reduction in wound radius indicates a 75% reduction in wound area in a circular wound.

Based on the examination below, the efficacy criterion was defined as "≥60% of subjects being responders." In a clinical study of trafermin (a drug for pressure ulcers and skin ulcers) in patients with diabetic ulcers (treatment for 8 weeks), 82.2% of subjects in the trafermin group (basic fibroblast growth factor [bFGF] 0.01% formulation group) were responders (i.e., subjects who achieved a ≥75% reduction in wound area).[17] In a clinical study of prostaglandin E1, a drug for skin ulcers (treatment for 8 weeks), 61.4% to 62.3% of subjects were responders (i.e., subjects who achieved a ≥75% reduction in wound area).[18] [redacted]

As for the primary endpoint, the proportion of responders was 80.9% (38 of 47 subjects) (95% CI: 66.7, 90.9) in the PPS and 79.6% (38 of 54 of subjects) (95% CI: 66.5, 89.4) in the FAS. Both values (80.9% and 79.6%) exceeded the efficacy criterion of 60%.

6.A.(1).3) Results of secondary endpoints

The following secondary endpoints were evaluated:

(a) Wound area and reduction (%) in wound area at the final evaluation

(b) Wound volume and reduction (%) in wound volume at the final evaluation

(c) Time course change in the greatest length of wound

(d) Time course change in wound score

(e) Time to judgement that wound closure is possible by secondary healing or by relatively simple surgical techniques

(f) Incidences of adverse events and malfunctions

The results of all secondary endpoints supported the effectiveness of wound treatment with the investigational device, and no investigational device-related adverse events were reported.

6.A.(1).3).(a) Wound area and reduction (%) in wound area at the final evaluation (LOCF)

In the PPS, the wound area (mean ± standard deviation [SD]) was 3.05 ± 2.76 cm^2 at baseline (Day 1), and significantly decreased to 0.98 ± 1.52 cm^2 4 weeks later (Day 29). Thereafter, the wound area continued to decrease over time to 0.61 ± 1.69 cm^2 at the final evaluation 8 weeks later (Day 57). In the FAS, the wound area was 3.49 ± 3.94 cm^2 at baseline (Day 1), and significantly decreased to 1.25 ± 2.39 cm^2 4 weeks later (Day 29). Thereafter, the wound area decreased over time to 0.89 ± 2.51 cm^2 at the final evaluation (Day 57). The reduction in wound area (mean ± SD) at the final evaluation (Day 57) was 72.8 ± 101.3% in the PPS and 71.0 ± 97.7% in the FAS. Student's t-test was used to compare values on Day 1 and Day 57 and the results indicated significant differences in both PPS and FAS ($P < 0.0001$).

6.A.(1).3).(b) Wound volume and reduction (%) in wound volume at the final evaluation (LOCF)

In the PPS, the wound volume (mean ± SD) was 1.35 ± 1.82 cm^3 at baseline (Day 1), and significantly decreased to 0.24 ± 0.51 cm^3 4 weeks later (Day 29). Thereafter, the wound volume decreased over time to 0.09 ± 0.27 cm^3 at the final evaluation (Day 57). In the FAS, the wound volume was 1.40 ± 1.88 cm^3 at baseline (Day 1), and significantly decreased to 0.28 ± 0.61 cm^3 4 weeks later (Day 29). Thereafter, the wound volume decreased over time to 0.14 ± 0.46 cm^3 at the final evaluation (Day 57). The reduction in wound volume (mean ± SD) on Day 57 was 92.7 ± 17.3% in the PPS and 92.6 ± 17.0% in the FAS. Student's t-test was used to compare values on

Day 1 and Day 57 and the results indicated significant differences in both analysis sets ($P < 0.0001$).

6.A.(1).3).(c) Time course change in the greatest length of wound (LOCF)

In the PPS, the greatest length of wound (mean ± SD) was 2.65 ± 1.25 cm at baseline (Day 1), and decreased to 1.27 ± 1.19 cm 4 weeks later (Day 29). Thereafter, the greatest length of wound decreased over time to 0.65 ± 1.02 cm at the final evaluation (Day 57). In the FAS, the greatest length of wound was 2.76 ± 1.33 cm at baseline (Day 1), and decreased to 1.36 ± 1.29 cm 4 weeks later (Day 29). Thereafter, the greatest length of wound decreased over time to 0.74 ± 1.13 cm at the final evaluation (Day 57). Student's t-test was used to compare values on Day 1 and Day 57 and the results indicated significant differences in both analysis sets ($P < 0.0001$).

6.A.(1).3).(d) Time course change in wound score (LOCF)

In the PPS, wounds were assessed using a scoring system based on 4 categories: exudates, inflammation/infection, granulation tissue, and necrotic tissue. For all categories, the scores at the final evaluation (Day 57) improved than baseline (Day 1) as shown in Table 12 (see the table for wound score definitions). In the exudate assessment, ≥90% of subjects had a score of 1 or 2 at baseline (Day 1), which decreased to approximately 40% at the final evaluation (Day 57). In the inflammation/infection assessment, ≥80% of subjects had a score of 0 at baseline (Day 1), which increased to ≥90% at the final evaluation (Day 57). In the granulation tissue assessment, ≥80% of subjects had a score of 1, 2, or 3 at baseline (Day 1), which decreased to approximately 40% at the final evaluation (Day 57). In the necrotic tissue assessment, ≥70% of subjects had a score of 0 at baseline (Day 1), which increased to ≥90% at the final evaluation (Day 57). Overall, wound scores rated by the investigator did not differ significantly from those rated by the independent review committee.

Table 12. Time course change in wound score*

			0	1	2	3	4	5
Exudates	Investigator	Day 1	1 (2.1%)	19 (40.4%)	26 (55.3%)	1 (2.1%)		
		Day 57	27 (57.4%)	15 (31.9%)	5 (10.6%)	0 (0.0%)		
	Independent	Day 1	1 (2.1%)	19 (40.4%)	26 (55.3%)	1 (2.1%)		
		Day 57	26 (55.3%)	16 (34.0%)	5 (10.6%)	0 (0.0%)		
Inflammation/infection	Investigator	Day 1	42 (89.4%)	5 (10.6%)	0 (0.0%)	0 (0.0%)		
		Day 57	46 (97.9%)	1 (2.1%)	0 (0.0%)	0 (0.0%)		
	Independent	Day 1	42 (89.4%)	5 (10.6%)	0 (0.0%)	0 (0.0%)		
		Day 57	46 (97.9%)	1 (2.1%)	0 (0.0%)	0 (0.0%)		
Granulation tissue	Investigator	Day 1	0 (0.0%)	17 (36.2%)	14 (29.8%)	8 (17.0%)	4 (8.5%)	4 (8.5%)
		Day 57	28 (59.6%)	17 (36.2%)	2 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Independent	Day 1	0 (0.0%)	16 (34.0%)	13 (27.7%)	10 (21.3%)	4 (8.5%)	4 (8.5%)
		Day 57	28 (59.6%)	17 (36.2%)	2 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Necrotic tissue	Investigator	Day 1	38 (80.9%)	8 (17.0%)	1 (2.1%)			
		Day 57	45 (95.7%)	2 (4.3%)	0 (0.0%)			
	Independent	Day 1	35 (74.5%)	11 (23.4%)	1 (2.1%)			
		Day 57	44 (93.6%)	3 (6.4%)	0 (0.0%)			

* The wound score classification was established based on the pressure ulcer assessment scale DESIGN 2002[19] published by Japanese Society of Pressure Ulcers.

	0	1	2	3	4	5
Exudates	None	Small amount	Moderate amount	Large amount		
Inflammation/ infection	No signs of local inflammation	Signs of local inflammation	Clear signs of local infection	Systemic impact		
Granulation tissue	Granulation cannot be assessed because the wound is healed or too shallow	Healthy granulation tissue accounts for ≥90%	Healthy granulation tissue accounts for ≥50% but <90%	Healthy granulation tissue accounts for ≥10% but <50%	Healthy granulation tissue accounts for <10%	No healthy granulation tissue exists
Necrotic tissue	No necrotic tissue	Soft necrotic tissue exists	Hard and thick necrotic tissue is attached to the wound			

6.A.(1).3).(e) Time to judgement that wound closure is possible by secondary healing or by relatively simple surgical techniques

In the PPS, time to judgement that wound closure is possible by secondary healing or by relatively simple surgical techniques was evaluated (Table 13; see descriptions in the table for the definitions of "wound closure by secondary healing" and "wound closure by relatively simple surgical techniques"). At the final evaluation (Day 57), 57.4% of subjects (assessed by the investigator) and 59.6% of subjects (assessed by the independent review committee) had wounds for which closure was judged to be possible by secondary healing, while 68.1% of subjects (assessed by the investigator) and 72.3% of subjects (assessed by the independent review committee) had wounds for which closure was judged to be possible by relatively simple surgical techniques. Time to judgement that wound closure is possible by secondary healing or by relatively simple surgical techniques was evaluated using the Kaplan-Meier method at the 25th percentile, 50th percentile, and 75th percentile. Time to judgement that wound closure is possible by secondary healing was 29.0 days (25th percentile), 57.0 days (50th percentile), and 58.0 days (75th percentile) as assessed by the investigator, and 29.0 days (25th percentile) and 57.0 days (50th percentile) as assessed by the independent review committee. Time to judgement that wound closure is possible by relatively simple surgical techniques was 18.0 days (25th percentile) and 43.0 days (50th percentile) as assessed by the investigator, and 19.0 days (25th percentile) and 41.0 days (50th percentile) as assessed by the independent review committee.

Table 13. Time to judgement that wound closure is possible by secondary healing or by relatively simple surgical techniques

	Wound closure is possible by secondary healing*		Wound closure is possible* by relatively simple surgical techniques**	
	Investigator	Independent review committee	Investigator	Independent review committee
The proportion of subjects with wounds for which closure was judged to be possible on Day 57 (%)	57.4	59.6	68.1	72.3
25th percentile (days) [95% CI]	29.0 [20.0, 41.0]	29.0 [15.0, 37.0]	18.0 [12.0, 26.0]	19.0 [14.0, 29.0]
50th percentile (days) [95% CI]	57.0 [34.0, 58.0]	57.0 [34.0, –]	43.0 [22.0, 55.0]	41.0 [24.0, 54.0]
75th percentile (days) [95% CI]	58.0 [–, –]	(75th percentile was not achieved)	(75th percentile was not achieved)	(75th percentile was not achieved)

* Definitions of wound closure by secondary healing and wound closure by relatively simple surgical techniques are as follows.

Closure by secondary healing	➢ The condition of the wound bed suggests that the wound can heal naturally. ➢ Treatment in this clinical trial is no longer necessary because the wound has healed.
Closure by relatively simple surgical techniques	➢ Healthy granulation tissue accounts for ≥75% of the wound. ➢ The bone, tendon, and vital organs are covered with granulation tissue. ➢ Local infection has been controlled in a clinically favorable manner. ➢ Very little necrotic tissue. ➢ Wound depth has decreased by ≥50% on average.

** Procedures such as skin grafting and suturing are assumed to be the relatively simple surgical techniques,

6.A.(1).3).(f) Incidences of adverse events and malfunctions

In total, 59 adverse events occurred in 32 subjects (incidence of adverse events, 59.3%) between baseline (Day 1) and the final evaluation (Day 57) or the day of discontinuation (Table 14). Among 15 subjects with events classified as infections and infestations, 1 had osteomyelitis chronic occurring at the wound site. The subject recovered after treatment with a concomitant drug, and the adverse event did not flare up again. This event was therefore considered unrelated to the investigational device. There were no adverse events for which a causal relationship to the investigational device could not be ruled out. Three cases of malfunctions of the investigational device (operational failure of centrifuge, insufficient centrifugation time of the bench-top centrifuge, and negative pressure failure of the blood collection tube) occurred in 3 subjects (incidence of malfunctions, 5.6%). These malfunctions did not cause adverse events that would impact users or subjects.

Table 14. Number of adverse events by symptom

		Number of events			Number of events
Overall		59	Injury, poisoning, and procedural complications		6
Eye disorders		1		Foot fracture	1
	Conjunctival hyperaemia	1		Subcutaneous haematoma	1
Gastrointestinal disorders		7		Wound	3
	Constipation	2		Heat illness	1
	Diarrhoea	1	Metabolism and nutrition disorders		4
	Enterocolitis	1		Hypoglycaemia	4
	Nausea	2	Musculoskeletal and connective tissue disorders		2
	Vomiting	1		Back pain	1
General disorders and administration site conditions		3		Spinal osteoarthritis	1
	Pain	1	Skin and subcutaneous tissue disorders		19
	Pyrexia	1		Decubitus ulcer	1
	Ulcer	1		Dermatitis contact	2
Infections and infestations		15		Eczema	4
	Cellulitis	1		Eczema asteatotic	1
	Cystitis	1		Hyperkeratosis	1
	Infection	1		Pruritus	4
	Localised infection	1		Rash	1
	Nasopharyngitis	4		Skin erosion	1
	Osteomyelitis	1		Skin exfoliation	1
	Osteomyelitis chronic	1		Urticaria	1
	Sycosis barbae	1		Diabetic ulcer	1
	Tinea pedis	1		Asteatosis	1
	Wound infection	1	Vascular disorders		2
	Catheter site infection	1		Haematoma	1
	Bacterial infection	1		Hypertension	1

6.A.(1).4) Evaluation of laboratory test values

Throughout the treatment period, the results of hematology tests, blood biochemistry tests, urine analyses, vital signs, standard 12-lead electrocardiograms showed no significant changes.

6.A.(2) Data on comparable overseas device

None of the reports on the comparable overseas device shown below denied the efficacy of wound treatment with the comparable overseas device, or revealed any serious adverse events associated with the comparable overseas device.

- A cohort analysis that evaluated wound healing outcomes in patients with chronic wounds from [redacted] 20[redacted] to [redacted] 20[redacted] showed that wounds in 91% (42 of 46) of patients healed within a mean of 9.8 weeks.[20]

- A report that evaluated wound healing outcomes in patients with chronic wounds from December 2008 to September 2010 showed that 86.3% and 90.5% of 285 wounds showed a 47.5% area reduction and a 63.6% volume reduction, respectively.[8]
- A report that evaluated wound treatment in patients with spinal cord injury from November 2008 to August 2010 showed that treatment was effective in 90% of patients with a mean area reduction of 53.8% and a mean volume reduction of 67.3%.[11]
- A post-marketing survey conducted from [redacted] 20[redacted] to [redacted] 20[redacted] showed no hematological, immunological, or other adverse events in patients with chronic wounds who were treated with the comparable overseas device.[21]

6.B Outline of the review conducted by PMDA

PMDA conducted reviews focusing on the following issues taking account of comments from the Expert Discussion:

(1) Conducting the Japanese clinical trial using an open label, uncontrolled, multicenter study design
(2) The efficacy and safety of the AutoloGel System
(3) Intended use or indication
(4) Post-marketing safety measures

6.B.(1) Conducting the Japanese clinical trial using an open label, uncontrolled, multicenter study design

Treatment with the AutoloGel System will be administered only to patients with wounds that have not responded to conventional treatment, and is not intended to replace or to be used in combination with conventional treatment; therefore, PMDA concluded that the applicant had no choice but to use an uncontrolled design (i.e., not using conventional treatment as a control) for the Japanese clinical trial. In Section "6.B.(2).2) Efficacy," the clinical significance of the effectiveness of wound treatment using the AutoloGel System was evaluated based on conventional treatment.

6.B.(2) The efficacy and safety of the AutoloGel System

6.B.(2).1) Difference between the AutoloGel System and the investigational device

There are differences in constituent parts between the AutoloGel System and the investigational device (Table 9), but the differences are not considered to affect the efficacy and safety evaluation of the AutoloGel System. PMDA therefore concluded it is acceptable to evaluate the efficacy and safety of the AutoloGel System based on the results of the Japanese clinical trial.

6.B.(2).2) Efficacy

In the Japanese clinical trial, the proportion of responders (i.e., subjects who achieved a 50% reduction in wound radius) exceeded 60%, the efficacy criterion. PMDA asked the applicant to explain (a) the reasons why the remaining 9 subjects did not achieve a 50% reduction in wound radius, and (b) the clinical significance of the proportion of responders in the Japanese clinical trial. The applicant's explanation is provided in the following sections.

6.B.(2).2).(a) Reasons that the 9 subjects did not achieve a 50% reduction in wound radius in the Japanese clinical trial

It is not clear why the 9 subjects did not achieve a 50% reduction in wound radius in the Japanese clinical trial. At the final evaluation (Day 57) in the granulation tissue assessment for wound score, 1 subject (Patient No.1 in Table 15) was rated as "2. healthy granulation tissue accounts for ≥50% but <90%," and 8 subjects (Patients Nos. 2 through 9 in Table 15) were rated as "1. healthy granulation tissue accounts for ≥90%." No exacerbation of exudates, inflammation, infection, or necrotic tissue was noted (Table 15). These findings suggest that the investigational device contributed to wound healing in all of the 9 subjects. Since 7 of 9 subjects were treated on an outpatient basis, there may have been difficulties in wound bed management.

Table 15. Percentage reduction in wound radius and wound scores of subjects who did not achieve a ≥50% reduction in wound radius

Patient	Time point	Wound radius reduction (%)	Wound score*							
			Investigator				Independent review committee			
			Exudates	Inflammation /infection	Granulation tissue	Necrotic tissue	Exudates	Inflammation /infection	Granulation tissue	Necrotic tissue
1	Day 1	−146.2	2	0	2	0	2	0	3	1
	Day 57		2	0	2	1	2	0	2	1
2	Day 1	36.9	1	0	4	0	1	0	4	0
	Day 57		1	0	1	0	1	0	1	0
3	Day 1	38.4	2	0	2	0	2	0	2	0
	Day 57		1	0	1	0	1	0	1	0
4	Day 1	−10.7	2	0	2	0	2	0	2	0
	Day 57		2	0	1	0	2	0	1	0
5	Day 1	35.7	2	0	1	0	2	0	1	0
	Day 57		1	0	1	0	1	0	1	0
6	Day 1	24.1	2	0	2	0	2	0	2	0
	Day 57		1	0	1	0	1	0	1	0
7	Day 1	26.5	2	0	3	0	2	0	3	0
	Day 57		2	0	1	0	2	0	1	0
8	Day 1	47.3	2	1	3	0	2	1	3	0
	Day 57		2	0	1	0	2	0	1	0
9	Day 1	26.0	0	0	2	0	0	0	3	1
	Day 57		0	0	1	0	1	0	1	0

* The smaller the wound score, the greater the improvement in the wound.

6.B.(2).2).(b) The clinical significance of the proportion of responders in the Japanese clinical trial

In the clinical study of trafermin, 82.2% of subjects were responders (i.e., subjects who achieved a ≥75% reduction in wound area). In the Japanese clinical trial, a slightly lower proportion of subjects (80.9%) were responders[17] (Table 16). The study population in the Japanese clinical trial were those with wounds that had not responded to conventional treatment including trafermin. This and other differences in the protocol preclude any direct comparison between the 2 studies. However, the proportion of responders in the Japanese clinical trial is not significantly different from that in the clinical study of trafermin. Therefore the observed efficacy of wound treatment with the investigational device is clinically meaningful.

Table 16. Comparison of the clinical study of trafermin with the Japanese clinical trial

	Clinical study of trafermin	Japanese clinical trial
Study population	• Diabetic ulcer • Aged ≥20 years • Target wound area ≤9 cm^2 (Superficial ulcers lower than Wagner Grade 2) • An ankle-brachial pressure index of ≥0.9	• Diabetic ulcer that has not responded to conventional treatment • Aged ≥20 years • Target wound area 1 cm^2-25 cm^2 • Skin perfusion pressure of ≥40 mmHg
Treatment period	8 weeks	8 weeks
Sample size	bFGF 0.01% formulation, 50 subjects (45 subjects*)	54 subjects (PPS, 47 subjects*)
Proportion of responders (i.e., subjects achieving a ≥75% reduction in wound area)	**bFGF 0.01% formulation group, 82.2%**	**80.9% (PPS), 79.6% (FAS)****
Proportion of patients with healed wounds	bFGF 0.01%, 66.7%	Closure by secondary healing (investigator's assessment): 57.4%

* Subjects in the efficacy analysis set
** If the wound is circular, a 50% reduction in wound radius (r) is equivalent to an approximately 75% reduction in wound area from baseline (Day 1).

6.B.(2).2).(c) Effects of prior trafermin treatment on the results of the Japanese clinical trial

The following data in the subgroups with and without prior trafermin treatment were compared:

(a) The proportion of responders (i.e., subjects who achieved a ≥50% reduction in wound radius)

(b) Percentage reduction in wound area

(c) The proportion of subjects with wound closure by secondary healing

The results suggested that prior trafermin treatment had no significant impact on the results of the Japanese clinical trial (Table 17). The proportion of responders (i.e., subjects who achieved a ≥50% reduction in wound radius) was 82.4% in the subgroup with prior trafermin treatment and 80.0% in the subgroup without. The mean percentage reduction in wound area was 88.5 ± 23.5% in the subgroup with prior trafermin treatment and 63.9 ± 125.5% in the subgroup without. The proportion of subjects with wound closure by secondary healing was 58.8% in the subgroup with prior trafermin treatment and 56.7% in the subgroup without as assessed by the investigator, and 64.7% in the subgroup with prior trafermin treatment and 56.7% in the subgroup without as assessed by the independent review committee. One subject without prior trafermin treatment had a wound that enlarged possibly due to chafing between the wound and a prosthesis. When this subject is excluded, the results in the subgroup without prior trafermin treatment are as follows:

- The proportion of subjects who achieved a ≥50% reduction in wound radius: 86.2 ± 30.2%.
- The proportion of subjects with wound closure by secondary healing: 58.6% (as assessed by both the investigator and the independent review committee).

Table 17. The proportion of responders, percentage reduction in wound area, and the proportion of subjects with wound closure by secondary healing, by prior trafermin treatment

Prior trafermin treatment	N	Proportion of responders (%)	Reduction in wound area Mean ± SD (%)	Subjects with wound closure by secondary healing (%)			
				Investigator		Independent review committee	
				Yes	No	Yes	No
Yes	17	82.4	88.5 ± 23.5	58.8	41.2	64.7	35.3
No	30	80.0	63.9 ± 125.5	56.7	43.3	56.7	43.3
No (1 subject excluded)*	29	82.8	86.2 ± 30.2	58.6	41.4	58.6	41.4

* Excluding 1 subject with a wound that enlarged possibly due to chafing between the wound and a prosthesis (−581.8% reduction in wound area).

PMDA's view:

Wound score and other assessment parameters indicated a trend towards improvement in the 9 subjects who did not achieve a 50% reduction in wound radius, as mentioned earlier. The above results do not suggest the ineffectiveness of wound treatment with the investigational device, and therefore do not deny the efficacy of the device (Table 15).

Although the differences in patient characteristics and study design preclude direct comparison of the data, the proportion of responders (80.9%) in the Japanese clinical trial did not differ significantly from the results of the clinical study of trafermin in patients with diabetic ulcers. Further, the effectiveness of treatment with the investigational device did not differ significantly between the subgroups with and without prior trafermin treatment in the Japanese clinical trial (Table 17). Taken together, the results of the Japanese clinical trial show the clinical significance of treatment with the AutoloGel System in patients with wounds that have not responded to conventional treatment.

The above findings show that wound treatment using the AutoloGel System has a certain clinical significance in patients with refractory ulcers such as diabetic ulcers.

6.B.(2).3) Safety

The safety evaluation data from the Japanese clinical trial revealed no adverse events for which a causal relationship to the investigational device could not be ruled out. In addition, there were no malfunctions that had a serious impact on subjects. Similarly, the clinical data on the comparable overseas device revealed no device-related adverse events. Based on the above, the safety of the AutoloGel System is ensured provided that the device is used in accordance with the proper use guidelines to be established by the relevant academic societies, which is discussed later.

6.B.(3) Intended use or indication

The proposed intended use or indication was "The AutoloGel System is intended to be used to

produce autologous platelet-rich plasma gel for promoting healing of wounds for which conventional treatment is not indicated." Based on the characteristics of the AutoloGel System and study population of the Japanese clinical trial, PMDA discussed whether the phrase "wounds for which conventional treatment is not indicated" was appropriate.

1) Based on the evaluation of the Japanese clinical trial, the indication of the AutoloGel System should be limited to patients with wounds that have not responded to conventional treatment; however, the results of the Japanese clinical trial were shown to be unaffected by conventional treatment; therefore, the range of conventional treatment need not be limited to pharmacotherapy or conservative treatment. The Japanese clinical trial enrolled patients with diabetic ulcers that had not responded to conventional treatment. Further, the applicant has not conducted a controlled study to compare the AutoloGel System with conventional treatment to evaluate wound healing effect, and thus has not evaluated the appropriateness of using the AutoloGel System as the first-line device for wound treatment. However, the Japanese clinical trial enrolled subjects with 2 different prior conventional treatment (those with trafermin treatment and those with conservative- treatment), and the results showed no significant difference between the subgroups with and without prior trafermin treatment in the effect of wound treatment using the investigational device (Table 17).

2) Patients should receive conventional wound treatment before using the AutoloGel System. However, the underlined parts of the phrase "wounds for which conventional treatment is not indicated" could lead to the misunderstanding that patients are not required to actually undergo conventional treatment before being treated with the AutoloGel System; therefore, the phrase should be replaced with "wounds that have not responded to conventional treatment."

3) The target disease of the Japanese clinical trial, "diabetic ulcers that have not responded to conventional treatment," is generally more refractory than other types of wounds. It is therefore acceptable to include non-diabetic ulcer type wounds that have not responded to conventional treatment in the indication of the AutoloGel System although such wounds were not evaluated in the Japanese clinical trial.

Based on the above, taking into account the comments from the Expert Discussion, PMDA concluded that the intended use or indication should be changed from the proposed text to the following: "The AutoloGel System is used to produce autologous platelet-rich plasma gel for

promoting healing of wounds that have not responded to conventional treatment."

6.B.(4) Post-marketing safety measures

6.B.(4).1) Proper use of the AutoloGel System

To ensure the efficacy and safety of the AutoloGel System, the method of proper use should be made widely known to healthcare professionals in the medical fields in which the AutoloGel System is expected to be used. PMDA asked the applicant to explain the plan to ensure proper use in Japan.

The applicant's response:

The proper use guidelines for the AutoloGel System will be prepared and released in cooperation with the Japanese Society for Foot Care and Podiatric Medicine (JFCPM). It is reasonable to ask JFCPM for cooperation because (a) the AutoloGel System is expected to be used mainly for diabetic ulcers and venous ulcers in the lower extremities, and (b) JFCPM consists of specialists from a variety of fields, meaning that the proper use can be examined from several perspectives. The proper use guidelines will include the following information: the significance of preparing the proper use guidelines, basic information such as products to which the guidelines apply, eligible patients, treatment period, precautions, and contraindications/prohibitions (Table 18).

Table 18. Summary of contents of the proper use guidelines of the academic society proposed by the applicant

<table>
<tr><th>Category</th><th>Summary</th></tr>
<tr><td>Eligible patients</td><td>Patients with wounds that have not responded to conventional treatment</td></tr>
<tr><td>Treatment period</td><td>Will include the information that the Japanese clinical trial evaluated the effect up to 8 weeks.</td></tr>
<tr><td>Precautions for use</td><td>➢ Efficacy in wounds accompanied by ischemia (blood circulation disorder) has not been established.
➢ Efficacy and safety have not been established in wounds previously treated with therapies other than the conventional treatments received by the subjects in the Japanese clinical trial.
➢ The duration of application of PRP prepared from blood collected at 1 time point should not exceed 1 week. Treatment may not be effective if PRP is applied for less than 24 hours.
➢ The precautions for use of each chemical agent should also be included in the precautions for the AutoloGel System.</td></tr>
<tr><td>Contraindications/ prohibitions</td><td>➢ Patients who meet any of the following criteria:
● Patients with hypersensitivity to any of the constituent parts of the AutoloGel System or ingredients of bovine origin
● Patients with wounds caused by malignant tumors
● Patients with wounds with active infections
● Patients who are known to have hypersensitivity to “calcium chloride,” an agent used in the AutoloGel System or “thrombin” derived from bovine blood; or patients in whom “calcium chloride” or “thrombin” derived from bovine blood is contraindicated.
➢ The following drugs should be listed as contraindications for coadministration.
<table>
<tr><th>Drug name, etc.</th><th>Clinical symptoms/treatment to be given</th><th>Mechanism/risk factors</th></tr>
<tr><td>Interaction with thrombin
Hemocoagulase (Reptilase)
Tranexamic acid (Transamin)</td><td>Thrombotic tendency may occur.</td><td>Procoagulants and antiplasmin agents promote thrombus formation, and coadministration will increase thrombotic tendency in an additive manner.</td></tr>
<tr><td>Interaction with thrombin
Aprotinin (Trasylol)</td><td>Thrombotic tendency may occur.</td><td>Aprotinin is an antifibrinolytic agent, and its thrombotic tendency will increase when coadministered with thrombin.</td></tr>
<tr><td>Interaction with calcium chloride
Digitalis preparations (e.g., digoxin)</td><td>Cardiac arrest may occur.</td><td>Calcium may enhance the action of digitalis preparations.</td></tr>
</table></td></tr>
</table>

PMDA’s view:

The applicant’s plan to release the proper use guidelines in cooperation with the relevant academic society is reasonable. Based on the Japanese clinical trial, the following information should also be provided in the proper use guidelines:

(1) “Wounds that have not responded to conventional treatment” means “wounds that show no trend towards reduction in wound area after ≥4 weeks of conventional treatment.”

(2) “Patients with wounds showing no trend towards reduction in wound area after treatment with the AutoloGel System” means “patients with wounds showing no improvements in terms of reduction in wound area or depth, or in condition such as granulation tissue formation and granulation tissue color tone after approximately 4

weeks of PRP gel treatment." If this applies to the patient, the physician should discontinue treatment with the AutoloGel System, and switch to another treatment. In the Japanese clinical trial, wound area and volume decreased significantly in 4 weeks after the start of treatment. If no reduction in wound area and volume is observed during this time period, wounds are not likely to respond to treatment with the AutoloGel System.

(3) The volume of blood drawn, volume of PRP, volume of PRP gel, and approximate wound area should be specified.

In addition, because the usage of the AutoloGel System should be made widely known in the medical fields in which the device is expected to be used, the applicant should ask for the cooperation of more than one academic society involved in wound treatment.

Based on the above, PMDA asked the applicant to take the following actions, and the applicant agreed:

(a) Add the information listed above in (1), (2), and (3) to the proper use guidelines.
(b) Request academic societies involved in wound treatment, in addition to JFCPM, to cooperate in the release of the proper use guidelines.
(c) Add the following statement to the "WARNINGS" section of the package insert: "The AutoloGel System should be used in accordance with the proper use guidelines developed by the relevant academic societies."

Multiple medical devices for separation of PRP have been approved in Japan, and there were no reports of adverse events caused by the usage of these devices in the Japanese clinical trial. Therefore, it is not necessary to establish standard requirements for physicians and medical institutions that use the AutoloGel System.

6.B.(4).2) Necessity of post-marketing use-results evaluation

Conclusion reached by PMDA concerning this issue is described in Section 7.

7. Plan for Post-marketing Surveillance etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

The applicant submitted a use-results survey plan (draft) to evaluate the safety and efficacy of treatment with the AutoloGel System in patients with wounds that have not responded to conventional treatment, with a planned sample size of 30 patients.

7.B Outline of the review conducted by PMDA

No device-related adverse events were reported in the Japanese clinical trial or clinical results of the comparable overseas device. In addition, there are no data showing safety concerns in the use of PRP centrifuges approved in Japan. PMDA concluded that no post-marketing use-results survey is necessary for the AutoloGel System.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. 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.

IV. Overall Evaluation

The AutoloGel System is a preparation kit for autologous platelet-rich plasma gel (a new term name is to be newly created) used to promote healing or dressing of wounds that have not responded to conventional treatment. The review of the AutoloGel System focused primarily on (1) the efficacy and safety of the AutoloGel System, (2) intended use or indication, and (3) post-marketing safety measures. Taking account of comments raised at the Expert Discussion, PMDA reached the conclusions shown below.

IV.(1) Efficacy and safety evaluation of the AutoloGel System

The performance tests demonstrated that platelets can be concentrated using the preparation method specified by the applicant including the centrifugation conditions. The rat skin defect model study suggested that PRP gel prepared with the AutoloGel System contributed to wound healing. The Japanese clinical trial demonstrated that wound treatment with the investigational device is effective for diabetic ulcers that have not responded to conventional treatment. A comparison of study results between the Japanese clinical trial and the clinical study of trafermin demonstrated the clinical significance of the efficacy of the investigational device shown in the clinical trial. No device-related adverse events were identified in data from the Japanese clinical trial or the comparable overseas device.

Based on the above, as discussed in IV.(2), the efficacy and safety of the AutoloGel System are

ensured provided that its indication is limited to “wounds that have not responded to conventional treatment.”

IV.(2) Intended use or indication

The results of the Japanese clinical trial demonstrated the effectiveness of the investigational device in the treatment of diabetic ulcers that had not responded to conventional treatment; however, efficacy in untreated wounds or efficacy in treatment in combination with conventional treatment have not been evaluated. The study enrolled not only subjects who had received prior conventional pharmacotherapy with trafermin but also subjects who had received conservative therapy as only prior treatment. The study results showed no significant difference in efficacy between the subgroups with and without prior trafermin treatment. Thus, PMDA considered that the indication of the AutoloGel System should be limited to wounds that have not responded to conventional treatment, but “the conventional treatment” need not be limited to pharmacotherapy or conservative treatment. Additionally, since “diabetic ulcers that have not responded to conventional treatment,” (the target disease of the Japanese clinical trial) is generally more refractory than other types of wounds, the indication of the AutoloGel System need not be limited to diabetic ulcers.

Based on the above discussions, PMDA concluded that the indication of the AutoloGel System should be “wounds that have not responded to conventional treatment” in the “Intended Use or Indication” section as discussed later.

IV.(3) Post-marketing safety measures

The details on the use of the AutoloGel System (e.g., how to select eligible patients and the wounds suitable for treatment; when to switch to another treatment) should be made widely known to healthcare professionals in the medical fields in which the AutoloGel System is expected to be used. Accordingly, PMDA confirmed that the applicant will issue the proper use guidelines in cooperation with multiple academic societies involved in wound treatment, and will include the following cautionary statement in the package insert: “The AutoloGel System should be used in accordance with the proper use guidelines developed by the relevant academic societies.” Multiple medical devices for separation of PRP have been approved and PRP preparation with the AutoloGel System does not require special techniques; therefore, it is not necessary to establish standard requirements for physicians and medical institutions that use the AutoloGel System. Since no device-related adverse events were reported in the Japanese clinical trial or in association with the use of the comparable overseas device, a post-marketing use-results

survey is not required.

Based on the above results, PMDA concluded that the AutoloGel System may be approved for the following intended use or indication.

Intended Use or Indication

The AutoloGel System is used to produce autologous platelet-rich plasma gel for promoting healing of wounds that have not responded to conventional treatment.

This product is classified as a biological product because one of its constituent parts contains thrombin of bovine origin.

PMDA has concluded that this application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

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