November 18, 2011
Office of Medical Device Evaluation
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Medical products 4, Orthopedic products
Term Name	Non-absorbable local hemostatic material for central circulation system
Brand Name	Matsudaito
Applicant	Sanyo Chemical Industries, Ltd.
Date of Application	June 14, 2010 (Application for marketing approval)

Results of Deliberation

In its meeting held on November 18, 2011, 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 with a re-examination period of 3 years. The product is classified as a specially controlled medical device and is not classified as a specially designated maintenance-and-management-required medical device, a biological product, or a specified biological product.

Review Report

October 28, 2011
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	Medical products 4, Orthopedic products
Term Name	Non-absorbable local hemostatic material for central circulation system (to be newly created)
Brand Name	Matsudaito
Applicant	Sanyo Chemical Industries, Ltd.
Date of Application	June 14, 2010
Reviewing Office	Office of Medical Devices I

Review Results

October 28, 2011

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Results of Review

Matsudaito is a non-absorbable local hemostatic material consisting of a sealant liquid (SC-625A) filled in a syringe, and accessory sheets and spatula.

The efficacy of Matsudaito was evaluated in a Japanese multicenter, randomized, controlled clinical study in patients who underwent thoracic aorta replacement. The study showed that Matsudaito was associated with a significantly higher hemostasis rate immediately before and 15 minutes after administration of protamine sulfate, which were the primary endpoints of the study, than conventional hemostatic procedures.

As for safety, the incidence of adverse events, including pleural effusion, pericardial effusion, and mediastinitis, tended to be higher in the Matsudaito group than in the control groups, albeit with no significant difference. These adverse events should not be taken lightly because only 55 subjects have used Matsudaito in the clinical study and these events may significantly affect the prognosis of patients.

Currently, therefore, the safety of Matsudaito is acceptable only if the following are met:

- The use of Matsudaito is limited to sites in which hemostasis cannot be achieved by conventional hemostatic procedures and the clinical study has demonstrated its efficacy and safety to some extent.
- Appropriate risk mitigation actions are taken, including dose restriction and a caution statement in the instructions for use.

Matsudaito was developed as a hemostatic material that can be used prior to heparin neutralization with protamine sulfate. For the reasons listed below, however, Matsudaito should not be used in patients with impaired blood coagulation prior to heparin neutralization unless its use is absolutely necessary because hemostatic procedure becomes difficult after heparin neutralization, or for other reasons. The usage of Matsudaito should thus be minimized.

(1) The clinical usefulness in patients (e.g., shortened operative duration and reduced blood loss) has not been confirmed.
(2) The hemostasis rate with Matsudaito tends to be higher after heparin neutralization, with a fewer number of additional hemostatic procedures, than prior to neutralization.
(3) Fewer anastomotic sites require hemostasis after heparin neutralization, which reduces the dose of Matsudaito.

Matsudaito is the first non-absorbable hemostatic material in Japan. Animal studies of Matsudaito showed persistent foreign-body reactions and the formation of fibrous membranes, which may lead to infection, at application sites. The submitted clinical study data involved only a limited number of patients. The Matsudaito group had a higher incidence of pleural effusion and pericardial effusion, which were probably related to Matsudaito, than the conventional treatment group. In addition, the long-term safety of applied Matsudaito has not been evaluated. For these reasons, it is important to collect information on the safety of Matsudaito, including the incidence, severity, causal relationship, etc. of pleural effusion, pericardial effusion, mediastinitis, infection, and pyrexia, as well as the efficacy of Matsudaito through the post-marketing surveillance.

As a result of its review, PMDA has concluded that Matsudaito 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 and Indication

Auxiliary hemostasis at the site of artificial vascular anastomosis associated with thoracic aorta replacement or branching artery arch replacement in which hemostasis cannot be achieved by usual surgical procedures including ligation

Review Report

October 28, 2011

I. Product for Review

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Term Name	Non-absorbable local hemostatic material for central circulation system (to be newly created)
Brand Name	Matsudaito
Applicant	Sanyo Chemical Industries, Ltd.
Date of Application	June 14, 2010
Proposed Intended Use	Hemostasis at the site of vascular anastomosis (between blood vessel and blood vessel, between blood vessel and artificial blood vessel, or between artificial blood vessel and artificial blood vessel)

II. Product Overview

Matsudaito is a non-absorbable local hemostatic material consisting of a sealant liquid (SC-625A) filled in a syringe, and accessory sheets and spatula (Figures 1 and 2). SC-625A is a viscous liquid consisting of a polyether-based fluorine-containing urethane prepolymer terminated with highly reactive isocyanate groups (-NCO). In the body, SC-625A reacts with the water in blood or on the body surface to polymerize sequentially while releasing carbon dioxide. The resulting gelatinous flexible polymer film closely adheres to the site of vascular anastomosis, thereby achieving hemostasis at the anastomotic site, independent of the patient's blood coagulation ability. This polymer film, which has an adequate elasticity and strength, tolerates the pressure of arterial blood and follows arterial pulsations.

Figure 1. Appearance of surgical sealant

Sheet

Spatula

Figure 2. Appearance of accessories

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

The data submitted for the present application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. The expert advisors present during the Expert Discussion on Matsudaito 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. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.(1) Origin or history of discovery

To achieve complete hemostasis at anastomotic sites in cardiovascular surgeries using an artificial heart-lung machine such as thoracic aorta replacement, first, heparin neutralization with protamine sulfate is required after the patient is removed from the artificial heart-lung machine. Hemorrhage after heparin neutralization is managed by additional suturing or astriction. Persistent hemorrhage from anastomotic sites is treated with absorbable local hemostatic materials, fibrin adhesives (pharmacological products), etc.

The following local hemostatic materials are approved in Japan: Absorbable local hemostatic materials (Arista AH, Approval number 22000BZX01241000, etc.), collagen-using absorbable local hemostatic materials (Avitene, Approval number 16000BZY00741000; Integran, Approval number 20700BZZ00468000, etc.), and gelatin-based absorbable local hemostatic materials (GRF Glue, Approval number 20700BZY00005000, etc.). The absorbable local hemostatic materials and collagen-using absorbable local hemostatic materials do not adhere to the tissue, and their hemostatic performance depends on the enhancement of platelet adhesion and coagulation. Therefore, these hemostatic materials are not effective in the presence of heparin or impaired blood coagulation function. GRF Glue, a gelatin-based absorbable local hemostatic material, adheres to the tissue, but causes tissue damage because it contains formaldehyde as a crosslinking ingredient. GRF Glue is therefore indicated only for the closure of the false lumen of the dissected aorta and for the hemostasis or closure at sutured anastomotic sites of the calcified aorta (including artificial blood vessels) associated with the closure of the false lumen, but not indicated for hemostasis at normal vascular anastomotic sites. On the other hand, fibrin adhesives (TachoComb, Approval number 22100AMX01699; Beriplast P, Approval number 22100AMX01695, etc.) are tissue-adhesive hemostatic materials. These contain blood-clotting ingredients and are generally used after heparin neutralization. They are, however, associated with the risk of viral infection caused by human plasma fractions used as a raw material, require a large amount of human blood, which is a precious raw material, and is not approved for hemostasis.

Matsudaito was developed to address the problems of the above hemostatic materials and adhesives. Matsudaito is a medical device intended to provide a hemostatic material that ensures hemostasis at anastomotic sites in the setting of impaired blood coagulation. Matsudaito meets the following requirements:

(a) The cured film is flexible and follows pulsations and other movements of the living soft tissue.

(b) A cured film is formed in a short period of time, which renders the surgical procedures more efficient.
(c) A cured film is formed and adheres to the tissue under the body's moist environment to stop hemorrhage.
(d) The risks of tissue toxicity and carcinogenicity are low.

SC-625A is a viscous, vehicle-free liquid consisting of (a) a polyether-based fluorine-containing urethane prepolymer (SC-625) with highly reactive isocyanate groups (-NCO) at both terminals of the hydrophilic polyether diol and (b) an antioxidant [redacted] (Figure 3).

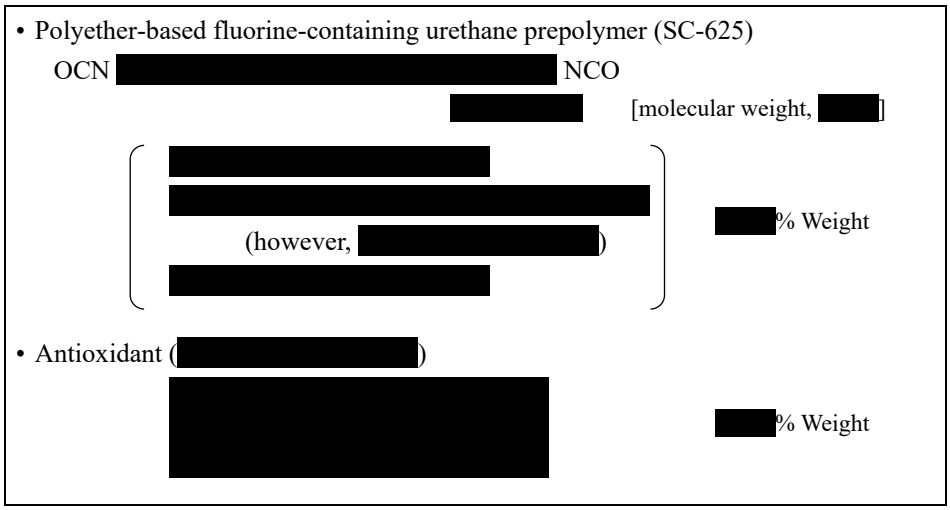

Figure 3. Composition of sealant liquid (SC-625A)

The isocyanate groups at both terminals react with the water in blood or on the surface of a living tissue in the body to convert to amino groups while releasing carbon dioxide. The amino groups react with the isocyanate groups in the unreacted prepolymer to form a urea bond (-NHCONH-), sequentially mediating polymerization to form a polyurethane compound (Figure 4). This gelatinous flexible polymer (water reactant) closely adheres to the body tissue to stop hemorrhage from vascular anastomotic sites.

$$OCN\text{-}R\text{-}NCO + H_2O \rightarrow [HOCONH\text{-}R\text{-}NCO] \rightarrow H_2N\text{-}R\text{-}NCO + CO_2 \uparrow$$

$$n\ OCN\text{-}R\text{-}NCO + n\ H_2N\text{-}R\text{-}NCO + (n+1)\ H_2O$$

$$\rightarrow H\text{-}(\text{-}HN\text{-}R\text{-}NHCO)_{2n-1}\text{-}HN\text{-}R\text{-}NH_2 + (n+1)\ CO_2 \uparrow$$

Figure 4. Polymerization reaction of urethane prepolymer

Sanyo Chemical Industries, Ltd. submitted the application for approval of Matsudaito for the indication of "Hemostasis at the site of vascular anastomosis (between blood vessel and blood vessel, between blood vessel and artificial blood vessel, or between artificial blood vessel and artificial blood vessel)."

1.(2) Use in foreign countries

There is no application submitted for approval of Matsudaito or no experience of using Matsudaito in foreign countries.

1.(3) Incidences of malfunctions of Matsudaito or similar medical devices

There is no experience of using Matsudaito or similar medical devices.

2. Specifications

The specifications for the characteristics/performance or function of Matsudaito were the appearance, viscosity, curing time, content of isocyanate groups, nuclear magnetic resonance spectra (^{1}H-NMR spectrum and ^{19}F-NMR spectrum), and infrared absorption spectrum of SC-625A. The specifications for the safety of Matsudaito were sterility assurance levels of the surgical sealant and accessories (sheets and spatula).

PMDA asked the applicant to explain whether the proposed performance and safety specifications were sufficient, and whether the proposed performance specification limits were appropriate.

The applicant's response:

Since the hemostatic cured film formed by Matsudaito needs to tightly adhere to the blood vessel to stop hemorrhage, the specifications includes sealing rate and pressure tolerance rate of the cured film, which are basic performance indices. Biological safety will be added to the safety specifications.

The viscosity and the content of isocyanate groups, which are likely to affect the performance of the cured film formed by Matsudaito, have been shown to change over time as SC-625A reacts with a trace amount of water remaining in the packaging container. For this reason, their specification limits (acceptance ranges) were determined based on the measured values of test samples that had a high hemostatic effect (complete hemostasis in 7 of 8 anastomoses) in a model of resected pig internal carotid artery, where achieving hemostasis with Matsudaito is more difficult than in the clinical setting. Animal and clinical studies have demonstrated the efficacy and safety of test samples that conformed to the proposed specifications, indicating that the limits and acceptance ranges of these specifications are appropriate.

Taken together with the results of the tests that demonstrated the appropriateness of the proposed specifications in Section "5. Performance," PMDA accepted the proposed specifications, including the limits.

3. Stability and Durability

To support the stability and durability of Matsudaito, the applicant submitted the results of long-term testing (25°C ± 2°C, 26 months) that assessed the long-term stability of SC-625A stored at room temperature after γ-ray irradiation at a standard dose (25 kGy), interim testing (30°C ± 2°C, 6 months) that assessed the effects of short-term storage at high temperature, and accelerated testing (40°C ± 2°C, 6 months). The applicant also submitted the results of long-term testing (25°C ± 2°C, 12 months) using γ-ray irradiation at the maximum dose ([redacted] kGy).

Long-term testing using γ-ray irradiation at the standard dose measured viscosity, curing time, content of isocyanate groups, nuclear magnetic resonance spectra (^{1}H-NMR and ^{19}F-NMR), and infrared absorption spectrum. Interim testing and accelerated testing measured viscosity, curing time, and content of isocyanate groups. All test samples conformed to the proposed specifications. Long-term testing using γ-ray irradiation at the maximum dose measured viscosity, curing time, content of isocyanate groups, nuclear magnetic resonance spectra (^{1}H-NMR and ^{19}F-NMR), and infrared absorption spectrum. All test samples conformed to the proposed specifications. On the basis of the above results, the applicant determined Matsudaito should be stored at room temperature with a shelf-life of 2 years.

PMDA reviewed the results of stability testing and confirmed that Matsudaito conformed to all of the specifications, including the additional specifications of the sealing rate and pressure tolerance rate of the cured film. PMDA agreed with the proposed shelf-life of 2 years at room temperature.

4. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act

The applicant submitted a declaration of conformity declaring that Matsudaito 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 the Pharmaceutical Affairs Act (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Announcement No. 122, 2005) and the Ministerial Ordinance on Quality Management System for Medical Devices and *In Vitro* Diagnostics (MHLW Ministerial Ordinance No.169 of 2004).

PMDA reviewed the conformity of Matsudaito to the Essential Principles and accepted the declaration.

5. Performance

5.(1) Studies to support safety

To support the safety of Matsudaito, the applicant submitted the results of a physicochemical study and a biological safety study.

5.(1).1) Physicochemical study

The physicochemical study tested the viscosity, content of isocyanate groups, nuclear magnetic resonance spectra (^{1}H-NMR and ^{19}F-NMR), and infrared absorption spectrum, which are included in the proposed specifications for Matsudaito, and its molecular weight and specific gravity. SC-625A conformed to the specifications for all tests.

PMDA reviewed the results of the physicochemical study and concluded that there was no particular problem.

5.(1).2) Biological safety

The biological safety of SC-625A was evaluated as shown below in compliance with the "Guidelines for Basic Biological Tests of Medical Devices and Medical Materials (in Japanese)" (PAB/MDD

Notification No. 99, dated June 27, 1995), the "Basic Principles of Biological Safety Evaluation Required for Application for Approval to Manufacture Medical Devices" (PFSB/ELD Notification No. 0213001, dated February 13, 2003), and the "Reference Data for Basic Principles of Biological Safety Evaluation (in Japanese)" (Administrative Notice/Medical Device Review No. 36, dated March 19, 2003).

In a reaction where SC-625 or SC-625A reacts with water to polymerize and form a film, unpolymerized prepolymers and low polymers co-exists. For this reason, the biological safety of Matsudaito was evaluated in a stepwise manner from Step 1 to Step 4.

Step 1: Basic toxicity of the raw materials (SC-625 and antioxidant [redacted])

SC-625, the primary active ingredient of SC-625A, was tested for its basic toxicity (cytotoxicity, genotoxicity [reverse mutation, chromosomal aberration, and micronuclei], acute systemic toxicity, sensitization, and short-term tissue reaction [short-term intramuscular implantation]). As for data regarding the basic toxicity of the antioxidant (redacted) added to SC-625A, the applicant submitted (a) a summary of the data that had been submitted to the U.S. Environmental Protection Agency by redacted, which manufactures redacted, (b) the toxicity data (acute toxicity, *in vivo* and *in vitro* genotoxicity, repeated-dose toxicity, reproductive toxicity, developmental toxicity/teratogenicity, and sensitization) in a report by a US government agency, and (c) the results of an additional sensitization test using the methodology recommended in Administrative Notice Medical Device Review No. 36.

Step 2: Toxicity of SC-625A (tests not performed in Step 1)

The short- and long-term safety of SC-625A, the final product made by adding redacted to SC-625, was investigated. Toxicity indices (intradermal reaction, pyrogenicity, hemolysis, and long-term local tissue reaction at implanted site and systemic toxicity [subacute and chronic toxicity]), other than basic toxicity tested in Step 1, were determined by directly implanting SC-625A in the body or using a SC-625A extract.

Step 3: Basic toxicity of the water reactant of SC-625A

To assess the basic toxicity of cross-linked polymers after completion of the reaction, a water reactant was newly manufactured and tested for its basic toxicity (cytotoxicity, genotoxicity [reverse mutation and chromosomal aberration], acute systemic toxicity, sensitization, and intradermal reaction).

Step 4: Other additional tests (toxicity of degradation products and thinning)

The tests up to Step 3 raised concerns about the repeated-dose systemic toxicity of the oxidative degradation product of the water reactant of SC-625 and about the thinning of blood vessels treated with SC-625A. To clarify these concerns, additional tests were conducted.

The applicant explained the results of these tests and toxicity information, and discussed the biological safety of Matsudaito based on positive test results.

The applicant's explanation:

(a) Genotoxicity, sensitization, and pyrogenicity

All of the tests conducted provided negative results.

(b) Systemic toxicity

SC-625 was tested for systemic toxicity. After intraperitoneal administration of SC-625 at the maximum dose of 2,000 mg/kg, 1 of 5 mice died. The 1,000 mg/kg group had only twisting of the lower back, but no death. The lethal dose lowest (LD_{LO}) for acute toxicity in mice was determined to be ≥1,000 mg/kg. The subacute and chronic toxicity study in rats, where Matsudaito was implanted subcutaneously, showed no evidence of systemic toxicity even at the maximum dose of 1,000 mg/kg. The no-observed-effect level (NOEL) for rats was determined to be ≥1,000 mg/kg.

The systemic toxicity of [redacted] was assessed based on the results of the repeated-dose (dietary admixture) toxicity study in dogs. The NOEL was determined to be 10,000 ppm in diet (= 10,000 μg/g in diet).

(c) Hemolysis

To evaluate the hemolytic toxicity, SC-625A was placed in direct contact with blood during the reaction process with water. The results demonstrated that SC-625A was "moderately hemolytic (hemolysis rate >10% and ≤20%)" at 1 hour of incubation and "mildly hemolytic (hemolysis rate >2% and ≤10%)" at 2 to 4 hours of incubation. SC-625A tested positive for hemolysis. On the other hand, gelatinized SC-625A after a reaction with water was "not hemolytic (hemolysis rate ≤2%)" at 1 and 2 hours of incubation, and "mildly hemolytic" only at 4 hours of incubation. Gelatinized SC-625A tested almost negative for hemolysis. Since Matsudaito immediately becomes gel on the contact surface and forms a film, almost no SC-625A molecules directly come in contact with the circulating blood. The effect of hemolysis temporarily caused by SC-625A is limited to its application site, and therefore, is not a clinically significant risk.

(d) Local tissue reaction

The intradermal reaction test of SC-625A showed a potent positive reaction. However, a negative result was obtained in a subsequent intradermal reaction test using a water reactant of SC-625A, which simulated the reaction in the body. In addition, the intramuscular implantation test showed no potent tissue reaction after 1-week tissue observation. The potent positive reaction in the intradermal reaction test was, therefore, considered temporary.

In an intramuscular administration study (4 weeks) and subcutaneous administration studies (4 weeks, 3 and 6 months, and 1 year), infiltration of inflammatory cells, pigment or mineral deposition (probably derived from hemoglobin), foamy histiocytes (possibly phagocytosis), and foreign-body giant cells were found in the surrounding tissue at Week 4. Subsequently, the tissue was covered with a fibrous capsule with a persistent weak tissue reaction. Almost all of these reactions resolved at Year 1. The gelatinized substance also tended to disappear.

In summary, Matsudaito causes a transient irritation reaction due to the chemical reaction in the early stage of application. However, the gelatinized polymer formed after the end of the reaction is covered by a thin fibrous capsule and then slowly phagocytized by macrophages (histiocytes), and eventually disappear. Matsudaito is therefore unlikely to cause a significant tissue reaction.

The short-term intramuscular implantation test investigated the local toxicity of low-molecular-weight substances, showing no tissue damage. The cytotoxicity test, which has a good correlation with a tissue irritation test and a better sensitivity, showed the half maximal inhibitory concentration (IC_{50}) of SC-625 (a prepolymer) was ≥5.0 mg/mL (colony formation rate at the maximum concentration of 5.0 mg/mL, 77.3%). Administrative Notice/Medical Device Review No. 36 states that (a) the IC_{50} of zinc dibutyldithiocarbamate (ZDBC) used as a positive control is 1.0 to 4.0 μg/mL, which is ≥1,000 times that of SC-625, and that (b) the IC_{50} of the extract of a polyurethane material containing 0.25% ZDBC (positive control B) is 40% to 80% (upper limit of causing muscular tissue irritation). On the basis of these results, unreacted SC-625A is estimated to have a very weak local toxic effect in humans. In summary, the local infiltration of the low-molecular-weight substances may occur early after the application of Matsudaito, but its local toxicity is minor.

(e) Metabolic fate of SC-625A

The phagocytized polyetherurethane is broken at the polyether chain by reactive oxygen released by macrophages.[1]-[3] The metabolic fate of polymers has been investigated. For example, polyvinylpyrrolidone with a molecular weight of ≤7,000 passes through the renal glomeruli, while the polymer with a molecular weight of ≥50,000 is not filtered and circulates in the body.[4]

SC-625A contains the antioxidant [redacted] to prevent oxidative degradation. The long-term implantation test showed that the gelatinized polymer tended to dissolve 1 year after implantation, suggesting that it is finally phagocytized by macrophages and broken down by oxidation. When SC-625, which contains no antioxidant, is immersed in water to make it water-soluble, its molecular weight is too low to be measured by gel permeation chromatography. In this water-soluble SC-625, polymers with a molecular weight of <1,000 are expected to be present at high proportions. SC-625 that has become water-soluble after being randomly oxidized and broken by macrophages is transferred by the circulating blood to the kidneys, passes through the glomeruli, and then is excreted from the body.

(f) Thinning of the arterial wall

Matsudaito was applied around the abdominal aorta of a rabbit to investigate whether a similar phenomenon to the thinning of the arterial wall caused by wrapping occurs. The aortic wall had a normal pressure at Month 3. The cured film of SC-625A is elastic enough to follow the contractions of the vessel so that excessive shear stress does not occur on the vascular wall.

(g) Rationale for maximum allowable dose of Matsudaito

Assuming that the mean body weight of Japanese people is 50 kg, the allowable limit of SC-625 is calculated to be 500 mg (1,000 mg/kg × 50 kg/100) at the safety factor of 100, based on the no observed adverse effect levels (NOAELs) determined in various mouse and rat studies. When the

usefulness of Matsudaito is not considered at all, the clinical dose of 0.5 g appears to be safe in terms of systemic toxicity. Assuming that a benefit factor of 10 is assigned to the clinical usefulness of Matsudaito, its safety is clinically acceptable up to 5 g. The NOEL of [redacted] was calculated from the NOEL (10,000 ppm in diet = 10,000 μg/g in diet) and the body weight of beagle dogs (16 kg, ISO 10993-17 Annex A), and the daily food consumption of beagle dogs (300 mg based on the information from the Division of Cellular and Molecular Toxicology, National Institute of Health Sciences). The tolerable daily intake (TDI) is 0.188 mg/kg/day assuming the safety factor of 1,000 (specified difference 10 × individual difference 10 × administration route difference 10). If SC-625 contains 30 mg/g of [redacted], the maximum total clinical exposure of [redacted] is 3.0 mg/kg in a human treated with 5 g of SC-625A who weighs 50 kg. This figure was converted to the daily dose, i.e., 3.0/(13 × 7) = 0.033 mg/kg/day, since SC-625A was continuously administered in a diet for 13 weeks in the repeated-dose study in dogs. This dose was lower than the TDI calculated from the dog's data and considered fully safe. The 28-day repeated-dose study of the oxidative degradation product of the water reactant of SC-625 (Step 4) showed the NOEL of 2,016 mg/kg as the total dose for 28 days. Assuming the human body weight of 50 kg and the safety factor of 100, the safety dose in humans is estimated to be 1,008 mg. This is twice the allowable limit (500 mg) of SC-625. The long-term implantation, subacute toxicity, and chronic toxicity studies of SC-625A showed no evidence of systemic toxicity, including the effect of phagocytosis on the lymph nodes, where SC-625A is transferred, or the renal effect of polymer filtration. The subacute repeated-dose study of the oxidative degradation product revealed no toxicological change in the kidneys. These results, and the discussion on biodegradation and excretion suggest that Matsudaito is safe up to the allowable limit of 5 g per body weight of 50 kg.

PMDA's view:
It is difficult to accept the applicant's rationale for the maximum allowable dose of Matsudaito because the benefit factor used in the explanation is not well founded. However, the animal tests that assessed the performance of Matsudaito showed no particular toxicological findings. The clinical study (up to 8.5 g) also showed no adverse events attributable to the toxicity of Matsudaito. On the basis of these results, the maximum allowable dose proposed by the applicant is acceptable. The animal study that evaluated the biological safety of Matsudaito demonstrated the formation of a fibrous capsule and persistent foreign body reactions at the application site. Since Matsudaito is not absorbed by the body, unlike the conventional hemostatic materials, it can contribute to persistent foreign body reactions and infection. The safety of Matsudaito should also be evaluated based on the results of the clinical study.

5.(2) Tests to support performance

5.(2).1) Verification of performance

To verify the performance of SC-625A, the following tests, including the curing time, the sealing rate, and water tolerance rate included in the specifications for Matsudaito, were specified:

(a) Test for reaction: Curing time
(b) Tests for adhesion strength: Adhesion strength and [redacted] adhesion strength to collagen, e-PTFE, polyester, and polyurethane.
(c) Tests for sealing performance: Sealing rate and pressure tolerance rate

(d) Tests for elasticity: [redacted] elasticity rate and [redacted]

Of these tests, (b) and (c) were comparative tests versus a fibrin adhesive (fibrin adhesive).

Approximately 56 seconds was required to cure a mixture of 1 g of SC-625A and 1 g of ion-exchange water. The mixture was cured within a practical and appropriate time frame.

The adhesion strength and [redacted] adhesion strength were specified in accordance with JIS K 6850:1999 in order to assess (1) the adhesiveness to living tissue or medical materials and (2) the adhesiveness to a blood vessel placed in the body. SC-625A had a very strong adhesiveness ([redacted]-[redacted] kgf/cm^2) to the adherends tested (collagen[redacted], e-PTFE, polyester, and polyurethane), regardless of their materials. On the other hand, the fibrin adhesive used as the control substance had a weak adhesiveness ([redacted]-[redacted] kgf/cm^2).

The sealing rate and pressure tolerance rate were established to evaluate the sealing and pressure tolerance properties of the cured film when blood pressure was applied. The cured film of SC-625A had the sealing rate of 100% and the pressure tolerance rate of 100%, indicating that the cured film does not leak blood or break under the normal blood pressure. On the other hand, the cured film of the fibrin adhesive had a high sealing rate (100%) but a low pressure tolerance rate (0%), suggesting that the film is weak and breaks.

The [redacted] elasticity rate and [redacted] ([redacted] elasticity rate) were measured to assess whether SC-625A can stretch or shrink with contraction of the vessel. They were [redacted]% and [redacted] kgf/cm^2, respectively, showing that SC-625A can stretch or shrink with contraction of the vessel.

These results demonstrate that Matsudaito has the necessary performance (curability, adhesiveness, hemostasis, and flexibility) to stop hemorrhage from the sutures of blood vessels or artificial blood vessels.

5.(2).2) Performance test

Matsudaito can stop hemorrhage (a) even when the blood coagulation ability is impaired in the presence of heparin and (b) from arteries. To verify this characteristic performance of Matsudaito, a performance test was conducted using a pulse pressure loading tester in comparison with the fibrin adhesive, the control substance.

First, SC-625A was applied on suture models (pig thoracoabdominal aorta, polyester artificial blood vessel, and e-PTFE artificial blood vessel). Then, heparinized [redacted] whole blood was passed through the models to create the pulse pressure of 120/60 mmHg at a cycle of 1 second. The hemostatic status was assessed immediately after the start of the test, and the blood loss for the first 15 minutes was measured. The results met the pre-defined acceptance limits (hemostasis rate 100%, blood loss ≤0.100 g). On the other hand, the fibrin adhesive had the hemostasis rate of 0% in all suture models, with the blood loss of 2.263 to 4.172 g.

PMDA's view:
The conditions of the tests submitted to support the performance of Matsudaito are appropriate to verify the basic performance of the cured film of Matsudaito that seals the sites of hemorrhage, but do not fully reflect the clinical use environment of Matsudaito, which is expected to be worse due to the presence of blood and body fluid. PMDA asked the applicant to explain why they consider that the performance test results assure the performance of Matsudaito required for clinical practice.

The applicant's explanation:
In the performance verification tests, 3 conditions that influence the performance of SC-625A (flexibility of the cured film, short-term film formation, and adhesiveness and hemostatic ability in a humid environment) were investigated based on reactivity, adhesion strength, sealing performance, elasticity, and pressure tolerance. The measured results are used as reference values in the specifications for Matsudaito.

The reactivity (curing time) of 56 ± 5 seconds was determined considering the maneuverability in clinical use. For the adhesion strength test, the limits of the adhesion strength and [redacted] adhesion strength between a material and Matsudaito were ≥[redacted] kgf/cm^2 and ≥[redacted] kgf/cm^2, respectively, for all of the test materials, to which Matsudaito is expected to be applied in clinical practice (vascular tissue [represented by collagen] and artificial blood vessels [e-PTFE, polyester, and polyurethane]). However, these limits themselves have no clinical significance. They are rather numerical indices to show that Matsudaito has a constant level of adhesiveness to each material. The sealing performance test assessed the sealing property and pressure tolerance of the cured film (static pressure 120 mmHg, 15 minutes). If the cured film has a profoundly poor sealing ability or pressure tolerance under the conditions of this test, Matsudaito is not expected to provide sufficient hemostasis in clinical use. The elasticity test was intended to investigate the stress-strain relationship by applying tension to the [redacted] cured film. The test is to verify that the cured film in a [redacted] condition has at least a similar dynamic flexibility to that of blood vessels. The limits of [redacted] elasticity rate and [redacted] have no clear clinical significance. They are numerical indices to show that Matsudaito has a constant level of flexibility. Nevertheless, the animal and clinical studies showed that SC-625A that conformed to these test specifications provided successful hemostasis. It is reasonable to determine that Matsudaito conforming to the performance test specifications can deliver a performance similar to that shown in the clinical study.

PMDA's view:
A worst-case scenario in the clinical environment should be studied for performance assessment to ensure the clinical efficacy and safety of Matsudaito. The pressure of "120/60 mmHg" used in the submitted test with a pulse pressure loading tester does not reflect the worst-case scenario. PMDA asked the applicant to clarify whether a higher load should be used in the test.

The applicant's explanation:
The above test used the normal blood pressure. Considering a patient with hypertension as the worst-case scenario, a pulse pressure loading test was conducted using a vascular anastomosis model

and artificial vascular anastomosis models (polyester and e-PTFE artificial blood vessels) at 180/120 and 220/160 mmHg. The test results were submitted. SC-625A met the predefined acceptance limits in all of the tests.

5.(2).3) Verification of appropriateness of specifications

To verify the appropriateness of the determined specification limits, a test was conducted using 3 batches of Matsudaito that conformed to the specifications and 2 batches of Matsudaito that did not conform to the specification limits of viscosity and content of isocyanate groups among the proposed specifications (viscosity, curing time, content of isocyanate groups, nuclear magnetic resonance spectra, and infrared absorption spectrum). This test was intended to show that the conformity of Matsudaito to each test specifications ensures that it has all of the required performance.

Among the performance verification tests, the elasticity test ([redacted] elasticity rate and [redacted]) and the test using a pulse pressure loading tester (hemostasis rate and blood loss) confirmed that all of the conforming and non-conforming products satisfied the predefined acceptance limits. Therefore products satisfying the specification limits can deliver the performance required for Matsudaito, and the specification limits are appropriate.

PMDA's view:

The specification limits or acceptance ranges should not be defined based on the results of tests using products not conforming to the specification limits of viscosity and content of isocyanate groups, because even such non-conforming products met the acceptance limit of each test used to support the performance of Matsudaito. In addition, as described above, the sealing and water tolerance tests selected to support the performance of Matsudaito did not reflect the method and environment for its clinical use. The results of these tests do not necessarily assure the required performance in clinical practice. PMDA asked the applicant to establish the specification limits and acceptance ranges based on the measured values of test samples that were shown to have the defined hemostatic performance in the animal and clinical studies of Matsudaito.

The applicant's response:

The specification limits of viscosity, content of isocyanate groups, hemostasis rate, and water tolerance rate were established based on each measured value of test samples that were shown to have a higher hemostatic performance than control samples in the "Controlled hemostatic experiment in a model of resected pig internal carotid artery," which has been selected to support the indication of Matsudaito. Thus, conformity to the proposed specifications ensures that Matsudaito has all of the required performance for clinical use.

PMDA reviewed the submitted data on the tests to support performance and accepted the applicant's response.

5.(3) Studies to support indication

To support the indication of Matsudaito, the applicant submitted the results of 5 animal studies in dogs, pigs, and rabbits.

5.(3).1) Hemostatic experiment in a model of dog internal carotid artery anastomosis

The hemostatic effect of SC-625 was investigated in a model of the resected internal carotid artery of male dogs (body weight, approximately 15 kg). The internal carotid artery was resected and anastomosed with suture of 4 stitches. SC-625 was applied all around the anastomotic site on projectile arterial hemorrhage from the anastomotic site under heparinization, and its hemostatic effect was evaluated based on the presence of hemorrhage 5 and 30 minutes after anastomosis. In the acute experiment (n = 3), the bilateral internal carotid arteries were subjected to the above procedures. Following evaluation 30 minutes after anastomosis, animals were sacrificed for gross observation of the anastomotic site from the lumen. In the subacute and long-term experiments (n = 1 for each), the left internal carotid artery was subjected to the above procedures. Angiography was performed to assess the stenosis of the anastomotic site at Month 3 in the subacute experiment and Month 16 in the long-term experiment. Then, animals were sacrificed for histological observation.

The acute, subacute, and long-term experiments showed no hemorrhage immediately and 30 minutes after resumption of the blood flow following single application of SC-625. The acute experiment revealed no infiltration of SC-625 into the lumen. In the subacute and long-term experiments, angiography showed no stenosis, obstruction, or pseudoaneurysm, gross observation showed no clear anatomical abnormality in the lumen at the anastomotic site, and histological observation showed no vascular intimal thickening. In the subacute experiment, the test substance remained as a gelatinous substance covering the anastomotic site. In the long-term experiment, the test substance was capsuled and covered by the membrane, and remained as it was, with the completely healed blood vessel at the anastomosis. A moderate adhesion was observed at the anastomosis. This was not adhesion between the blood vessel and the test substance, but the adhesion between the tissue covering the test substance and the surrounding tissue. The test substance itself could easily be removed from the blood vessel. After removal of the test substance from the blood vessel, neither adhesion nor hardening associated with inflammation was seen on the outer surface of the blood vessel, suggesting that the long-term adhesion of the test substance caused no problem.

5.(3).2) Hemostatic experiment in a model of pig coronary arterial bypass operation

The hemostatic effect, etc. of SC-625A was investigated in a model of pig coronary arterial bypass operation. Male domesticated pigs (body weight, approximately 30 kg) at the age of 16 weeks were divided to the acute test group (n = 8) or the chronic test group (n = 4). The left internal thoracic artery was anastomosed to the coronary artery (left anterior descending branch) with suture of 4 stitches. Then, SC-625A was applied all around the vascular anastomotic site to stop projectile arterial hemorrhage from the anastomotic site under heparinization. The anastomotic site was observed 5 minutes after SC-625A application to confirm hemostasis. The root of the left anterior descending branch was ligated to measure the blood flow in the left internal thoracic artery. Hemodynamics and electrocardiogram were monitored for 30 minutes. The anastomotic site was observed for hemostasis 30 minutes after SC-625A application. In the acute test group, hemostasis at the anastomotic site was confirmed, and then animals were subjected to catheterization of the anastomotic site and thereafter sacrificed for gross observation to check whether the test substance was infiltrated into the lumen. In the chronic test group, hemostasis at the anastomotic site was confirmed 30 minutes after SC-625A

application, and then the chest was closed; the animals were subjected to angiography of the anastomotic site at Week 8 (n = 2) and Week 18 (n = 2), and thereafter sacrificed for gross observation of the lumen at the anastomotic site. Longitudinal images of the lumen showed no infiltration of SC-625A into the vascular lumen.

The acute and chronic experiments showed complete hemostasis with single application of SC-625A, with no hemorrhage 30 minutes after application. No infiltration of SC-625A into the lumen at the anastomotic site was observed. The chronic experience revealed neither stenosis nor obstruction at the anastomotic site at Weeks 8 and 18. Histological observation at Week 18 confirmed that the epidermis of the lumen at the anastomotic site was covered by a layer of regenerated cells (probably intimal cells), without intimal thickening. Stenosis in the left internal thoracic artery was found in 1 animal in the chronic experiment. This stenosis was located approximately 15 mm from the anastomotic site where SC-625A was applied. Anatomical findings also suggested no relationship between the stenosis and the anastomotic site.

5.(3).3) Hemostatic experiment in a model of pig descending aorta replaced with artificial blood vessel

The hemostatic effect of SC-625A was investigated in a model of pig descending aorta replaced with artificial blood vessel. After placement of an aortic cross-clamp, a part of the descending aorta of 2 male domesticated pigs (body weight, approximately 30 kg) at the age of 11 weeks, was replaced by an artificial blood vessel (polyester), which was anastomosed to the original aorta at 2 sites, proximal and distal to the graft. After removal of the clamp, the proximal anastomotic site was observed for hemorrhage only from the needle holes. After re-closure, SC-625A was applied on a silicone sheet. The anastomotic site was wrapped around with this silicone sheet for 5 minutes. Then, the silicone sheet alone was removed (silicone sheet transfer method). The anastomotic site was observed for hemostasis. This procedure was repeated until complete hemostasis was achieved. Once complete hemostasis was achieved, the anastomotic site was again observed 30 minutes later to confirm complete hemostasis. Then, the distal anastomotic site was observed for hemorrhage only from the needle holes and subjected to the same procedures as the proximal anastomotic site.

At the proximal anastomotic site, the 2 animals achieved complete hemostasis both immediately and 30 minutes after resumption of the blood flow. At the distal anastomotic site, 1 animal achieved complete hemostasis both immediately and 30 minutes after resumption of the blood flow. The other animal had a slight blood leakage immediately after resumption of the blood flow. After the initial test substance was removed from this animal, the new one was applied to the anastomotic site. After the second application, the animal achieved complete hemostasis both immediately and 30 minutes after resumption of the blood flow.

5.(3).4) Hemostatic experiment in a model of resected pig internal carotid artery

The superiority of SC-625A to a fibrin adhesive in hemostatic effect was investigated in a model of a resected pig internal carotid artery. The bilateral internal carotid arteries of 4 male domestic pigs (body weight, approximately 30 kg) were resected (8 sites in total) and anastomosed with suture of 3 to 4 stitches. The hemostatic effect of the fibrin adhesive and SC-625A on projectile arterial hemorrhage

from the anastomotic site under heparinization was evaluated. First, approximately 0.4 g of the fibrin adhesive, the control substance, was applied. Its hemostatic effect was assessed 3 minutes later. The blood loss was measured during an appropriate period of time (i.e., 5 seconds to 30 minutes) depending on the blood loss level. The measured blood loss was converted to the blood loss over 30 minutes. After removal of the control substance from the blood vessel, the anastomotic site was rinsed with physiological saline. Then, approximately 0.2 g of SC-625A was applied to the anastomotic site by the silicone sheet transfer method. The silicone sheet was removed 3 minutes later while spraying physiological saline, and the hemostatic effect and the blood loss were assessed in the same manner as above.

When the fibrin adhesive was used to stop arterial hemorrhage at the mean blood pressure of 106/70 mmHg, the adhesive was peeled off after resumption of the blood flow, resulting in projectile hemorrhage in all animals. A single application of SC-625A provided complete hemostasis at 7 of 8 anastomotic sites in 3 minutes. A slight blood leakage was seen at the remaining 1 site, but it was completely stopped by short-term astriction. At all sites, complete hemostasis was achieved in 30 minutes after resumption of the blood flow. The blood loss over 30 minutes after resumption of the blood flow was 4.1 ± 2.2 g with SC-625A, which was due to blood leakage only from tissues other than the anastomotic sites. The blood loss with SC-625A was profoundly smaller than that after treatment with the fibrin adhesive (5,512.5 ± 2,784.7 g).

5.(3).5) Hemostasis and histology in a model of longitudinally resected rabbit common carotid artery

Pathological changes at a blood vessel wound were mainly investigated after SC-625A was used to stop arterial hemorrhage. The right common carotid arteries of 12 rabbits (weight 2.8-3.1 kg) at the age of 13 to 15 weeks were longitudinally resected in approximately 1 cm. After the center of the incision was sutured with 1 stitch, SC-625A was applied to the incision for hemostasis. After SC-625A application for 3 minutes, a lactated Ringer's solution was applied to promote polymerization. Approximately 2 minutes later, the incision was macroscopically observed for hemostasis. Then, 3 animals each were euthanized at Weeks 1, 6, 15, and ≥26 (4 groups). The right common carotid artery was isolated from each animal for histological observation.

All animals achieved complete hemostasis. Histology at Week 1 revealed blood clots on the vascular adventitia covering the incision of the blood vessel and SC-625A covering the blood clots. No infiltration of SC-625A into the incision of the blood vessel was observed. The blood clots had a mononuclear cell infiltrate and fibroblasts. Histology at Week 6 revealed no blood clot. The missing part of the blood vessel had vascular endothelial cells and connective tissue cells, on which continuous collagenous fibers and an epithelial cell layer were formed at the incision site. Histology at Week 15 revealed the thickened epithelial cell layer at the incision site and vascular endothelial cells starting differentiation, with the formation of elastic fibers. At and after Week 26, both vascular endothelial cells and elastic fibers were observed, suggesting the recovery of the vascular wall close to a histologically normal state.

SC-625A was covered by mononuclear cells and fibrous cells at Week 1. The same condition was observed at the incision site at Weeks 6, 15, and ≥26.

PMDA's view:
The data on the tests to support the indication of Matsudaito showed that the high hemostatic performance of Matsudaito was verified in the tests using the animal models that reflected its clinical use environment. However, Matsudaito was covered by mononuclear cells even 26 weeks after its application. This possibly suggests persistent infection or foreign body reactions. In particular, a gap between Matsudaito and the fibrous tissue covering Matsudaito can be a hotbed for infection. There is the concern that the gap may contribute to an increased risk of infection in the clinical use of Matsudaito. The risk of inflammation or infection associated with Matsudaito, a non-absorbable hemostatic material, remaining in the body must be assessed based on comprehensive data including the clinical study results of Matsudaito.

5.(4) Studies to support directions for use

To support the directions for use of Matsudaito, the applicant submitted the data on the dosage and a saturated swelling test of Matsudaito.

5.(4).1) Dosage

The dosage per anastomosis when SC-625A is applied all around a blood vessel is indicated by the following equation: "Dosage (g) per anastomosis × Circumference of the blood vessel (mm) / Length of the incision at the anastomotic site (mm)." The results of the pulse pressure loading test using the polyester and e-PTFE artificial blood vessel suture models were submitted to support the performance of Matsudaito. The test results revealed that 100% hemostasis was achieved by the circumferential application of SC-625A to the polyester or e-PTFE artificial blood vessel that was partially incised and then sutured [see Section "5.(2).2) Performance test"]. In this test, the artificial blood vessel diameter was 14 mm (polyester) and 6 mm (e-PTFE), the incision length was 10 mm (polyester) and 5 mm (e-PTFE), and the mean dosage per anastomosis was 0.17 g (polyester) and 0.07 g (e-PTFE). The mean circumferential dosage per anastomosis (equivalent dosage) was 0.75 g (polyester) and 0.27 g (e-PTFE). From these figures, the following correlation equation for the dosage per anastomosis and the vascular diameter is obtained when SC-625A is applied all around the blood vessel: "Circumferential dosage (g) per anastomosis = 0.052 × Vascular diameter (mm)."

In addition, the clinical study showed a high hemostasis rate in the SC-625A group (immediately before administration of protamine sulfate, 79.1%; 15 minutes post-dose, 88.3%). The mean dosage of SC-625A used for 198 anastomoses was 0.80 mL (0.98 g). In the clinical study, the vascular diameter was not measured. Assuming that the vascular diameter was 25 mm at the proximal and distal anastomotic sites and 10 mm at all other anastomotic sites,[1] the mean diameter was estimated to be 18.6 mm. The circumferential dosage per anastomosis for a blood vessel with a mean diameter of 18.6 mm was calculated to be 0.95 g using the correlation equation established based on the results of the performance test. Since this figure does not profoundly differ from the mean dosage of 0.80 mL

[1] In general, the vascular diameter at anastomotic sites (proximal and distal anastomotic sites) of a great vessel is 20 to 30 mm, while that at anastomotic sites of other blood vessels in thoracic aorta replacement is 5 to 15 mm. Their means were used in the above calculation.

(0.98 g) in the clinical study, the applicant determined that the dosage calculated using the correlation equation could be used as a guide in determining the clinical dosage of Matsudaito.

5.(4).2) Saturated swelling test

The saturated swelling ratio of SC-625A was measured. SC-625A absorbed and swelled up to approximately 2.5 times its own weight.

PMDA's view:

The applicant explained that the dosage calculated using the correlation equation could be used as a guide in determining the clinical dosage of Matsudaito, because the "circumferential dosage per anastomosis" calculated using the correlation equation established based on the animal test results did not profoundly differ from the mean dosage in the clinical study. In the clinical study, however, whether each subject received circumferential application of SC-625A by the silicone sheet transfer method is unknown. From a safety viewpoint, the dosage of Matsudaito should be the necessary minimum. For these reasons, it is not appropriate to determine the clinical dosage of Matsudaito using the correlation equation of the vascular diameter. The dosage of Matsudaito should be assessed based on comprehensive data including the clinical study results of Matsudaito. It should be further discussed in the Clinical Study section [see Section "8.B.(4) Directions for use and risk mitigation actions"].

6. Risk Analysis

The applicant submitted a summary of risk management, the risk management system, and its implementation status of Matsudaito in accordance with ISO 14971 "Medical devices - Application of risk management to medical devices." Risk analysis for important hazards and risk mitigation was performed and hazards that required risk mitigation were identified. The applicant submitted a summary of the results of risk mitigation of the hazards, foreign body reactions, and postoperative infection.

PMDA reviewed the data on risk analysis and accepted them.

7. Manufacturing Process

The applicant submitted the data on the manufacturing process, manufacturing facilities, sterilization (γ radiation), and quality control of Matsudaito.

PMDA reviewed the submitted data on the manufacturing process and accepted them.

8. Clinical Data

The applicant submitted the results of a Japanese study that evaluated the hemostatic effect of SC-625A at anastomotic sites.

8.A. Outline of the clinical study

8.A.(1) Study to evaluate hemostatic effect of SC-625A at anastomotic sites (study period, [redacted] 20[redacted] to [redacted] 20[redacted])

A multicenter, open-label, randomized, controlled study was conducted to evaluate the efficacy and safety of Matsudaito versus conventional surgical procedures in hemostasis at anastomotic sites during thoracic aorta replacement at 6 study sites in Japan (target sample size, 90 subjects in total [60 in the Matsudaito group, 30 in the control group]).

The major inclusion criteria were patients aged ≥20 and <80 years who planned to undergo thoracic aorta replacement (excluding ruptured aneurysm, acute dissection, and aortic root replacement [Bentall procedure and valve-sparing aortic root replacement]). The following patients were excluded from the study:

- Patients with coagulation or fibrinolytic system abnormalities (fibrin degradation products [FDP] level of 30 μg/mL [or FDP-E of >210 ng/mL] or platelet count of <100,000/mm^3)
- Patients with severe anemia (hemoglobin [Hb] of <9.0 g/dL)
- Patients with serious complications involving the liver (total bilirubin >3.0 mg/dL), kidney (creatinine >2.0 mg/dL), or lung (forced expiratory volume in 1 second <1.0 L, arterial O_2 pressure [PaO_2] [room air] <60 mmHg, or percutaneous arterial oxygen saturation [SpO_2] [room air] <90%)
- Patients with diabetes (HbA_{1C} >8.0%)

The major surgical procedures in the study are shown below. Procedure (d) was performed only in the Matsudaito group but not in the control group.

(a) The subject received heparin after the completion of replacement. Then, extracorporeal circulation was resumed.
(b) The blood flow was blocked to start vascular anastomosis.
(c) After vascular anastomosis, the blood flow was resumed to observe any surgical hemorrhage requiring additional sutures or anastomosis. When surgical hemorrhage was present, additional sutures were inserted.
(d) In the Matsudaito group, the blood flow was blocked and Matsudaito was applied to anastomotic sites without surgical hemorrhage. Matsudaito was applied at a dose of approximately 0.5 g per anastomotic site by a direct or transfer method. The silicone sheet was removed. After the blood flow was resumed, the blood vessel was observed for any hemorrhage. If hemorrhage was present, Matsudaito was applied again.
(e) For each anastomotic site, procedures (b) to (d) were repeated.
(f) After the completion of anastomosis at all sites, all of the anastomotic sites were observed for hemostatic status. If hemorrhage was present, the Matsudaito group received Matsudaito again or additional sutures, or the control group received necessary interventions such as additional suturing.
(g) The subject was removed from the extracorporeal circulation and observed for any hemorrhage at the anastomotic sites immediately before administration of protamine sulfate.
(h) Protamine sulfate was administered. The control group received additional hemostatic procedures if hemorrhage was present.

(i) The anastomotic sites were observed for any hemorrhage 15 minutes after administration of protamine sulfate.
(j) The subject received additional hemostatic procedures if hemorrhage was present.

In the Matsudaito group, additional hemostatic procedures with fibrin products or conventional medical devices (e.g., absorbable local hemostatic materials) within 15 minutes after protamine sulfate administration were prohibited. Hemostatic procedures with fibrin products or conventional medical devices (e.g., absorbable local hemostatic materials) were allowed only when hemorrhage could not be stopped by application (including re-application) of Matsudaito, additional suturing after protamine sulfate administration, or application of Matsudaito after 15 minutes following protamine sulfate administration. The Matsudaito group received Matsudaito at all anastomotic sites in principle. However, because surgeons had to perform this unfamiliar procedure at a site not easily accessible (aortic arch replacement at a distal site), subjects who required replacement at a distal site were allowed to receive conventional hemostatic procedures to ensure their safety. If this was the case, conventional hemostatic procedures were permitted as an exception and the use of Matsudaito was prohibited. Those subjects were excluded from statistical analyses. On the other hand, the control group received well-established institutional standard surgical procedures since no hemostatic material has an established efficacy in the presence of heparin in thoracic aorta replacement. The control group was prohibited from using Matsudaito, but did not have any other prohibitions including the use of other hemostatic materials.

The primary efficacy endpoints were “hemorrhage at each anastomotic site immediately before protamine sulfate administration” and “hemorrhage at each anastomotic site 15 minutes after protamine sulfate administration.” The secondary endpoints were the “time from the start of protamine sulfate administration until the end of surgery,” “blood loss (total amount of blood absorbed by gauze from the beginning to the end of surgery, Cell Saver return volume, and drain blood loss for the first 8 hours after the start of draining following the entry in ICU),” “intraoperative transfusion volume (packed red blood cells, frozen plasma, and platelet),” and “any additional hemostatic procedure at each anastomotic site after protamine sulfate administration and its details.” The safety of Matsudaito was evaluated up to Month 6 based on the results of “postoperative examination of anastomotic sites (chest CT scan),” “signs and symptoms,” “pyrexia,” and “general laboratory tests.”

Of 86 subjects enrolled in the study (59 in the Matsudaito group, 27 in the control group), 4 subjects in the Matsudaito group were discontinued from the study prior to the surgery (postponed surgery in 2 subjects, exclusion criteria violation [conventional surgery using no Matsudaito in the test group] in 2 subjects). The remaining 82 subjects who underwent aorta replacement (55 in the Matsudaito group, 27 in the control group) were included in full analysis set (FAS), which was used for safety analysis. In efficacy analysis, the primary endpoints and a secondary endpoint (i.e., any additional hemostatic procedure) were evaluated per anastomotic site. The other secondary endpoints were evaluated per subject. Of the 82 subjects in the FAS, 81 (54 in the Matsudaito group, 27 in the control group) were included in per protocol set (PPS), and the remaining 1 subject in the Matsudaito group was excluded because of a protocol deviation. The PPS was used for efficacy analysis. Of 353 anastomotic sites (231 in the Matsudaito group, 122 in the control group) in the FAS, 6 anastomotic sites were excluded from

efficacy analysis because they were in the subject excluded from the efficacy analysis. Further, the following 34 anastomotic sites (29 in the Matsudaito group, 5 in the control group) were excluded: 10 unevaluable anastomotic sites (5 in each group), 9 anastomotic sites that underwent exceptional hemostatic procedures (Matsudaito group), and 15 anastomotic sites, to which Matsudaito could not be applied (Matsudaito group). As a result, 313 anastomotic sites (196 in the Matsudaito group, 117 in the control group) were included in the PPS, which was used in efficacy analysis of anastomotic sites.

The age of subjects (mean ± standard deviation) was 67.6 ± 10.3 years old in the Matsudaito group and 67.1 ± 7.1 years old in the control group. The sex, diagnosis, planned surgery, complications, and other patient characteristics did not differ between the Matsudaito and control groups.

A total of 8 subjects (4 in the Matsudaito group, 4 in the control group) were withdrawn from the study during the follow-up period up to Month 6 for the following reasons: Death (3 in the Matsudaito group, 2 in the control group) and missing Month 6 examination (1 in the Matsudaito group, 2 in the control group).

Table 1 shows the number of subjects and anastomotic sites that underwent each replacement in the efficacy analysis populations.

Table 1. Summary of aortic replacement

Replacement surgery	Number of subjects			Number of anastomotic sites		
	Matsudaito	Control	Total	Matsudaito	Control	Total
Ascending aorta replacement	12	5	17	26	11	37
Ascending aorta replacement + partial aortic arch replacement	2	0	2	7	0	7
Partial aortic arch replacement	2	0	2	6	0	6
Total aortic arch replacement	26	16	42	130	88	218
Total aortic arch replacement + descending aorta replacement	0	1	1	0	6	6
Descending aorta replacement	12	5	17	27	12	39
Total	54	27	81	196	117	313

Table 2 shows the results of the primary efficacy endpoints of “hemorrhage at each anastomotic site immediately before protamine sulfate administration” and “hemorrhage at each anastomotic site 15 minutes after protamine sulfate administration.” Matsudaito had a higher efficacy with statistical significance.

Table 2. Hemostasis rate immediately before and 15 minutes after protamine sulfate administration

	Matsudaito	Control	*P*-value*
Immediately before protamine sulfate administration	79.1% (155 of 196 anastomotic sites)	38.5% (45 of 117 anastomotic sites)	<0.001
15 min after protamine sulfate administration	88.3% (173 of 196 anastomotic sites)	60.7% (71 of 117 anastomotic sites)	<0.001

* Fisher’s exact test

The secondary efficacy endpoints of the time from the start of protamine sulfate administration until the end of surgery, the blood loss, and intraoperative transfusion volume showed no statistically significant difference between the groups (Table 3). The Matsudaito group had a significantly lower percentage of subjects who required any additional hemostatic procedure than the control group. Also,

the Matsudaito group had a significantly lower percentage of anastomotic sites that required additional sutures, fibrin products, conventional medical devices, or others (Table 4).

Table 3. Time from the start of protamine sulfate administration until the end of surgery, blood loss, and intraoperative transfusion volume

	Matsudaito (n = 53)*[1]	Control (n = 27)	*P*-value*[3]
Time from the start of protamine sulfate administration until the end of surgery	137.3 min	140.6 min	0.815
Amount of blood absorbed by gauze	748.8 g	674.8 g	0.453
Cell Saver return volume	220.4 mL	378.2 mL	0.423
Drain blood loss	473.2 mL*[2]	391.1 mL	0.252
Packed red blood cell transfusion volume	5.7 U	6.4 U	0.535
Frozen plasma transfusion volume	6.0 U	8.4 U	0.057
Platelet transfusion volume	7.4 U	9.3 U	0.407

*[1] One subject was excluded from the efficacy analysis population of 54 subjects.
*[2] Two subjects were excluded from the efficacy analysis population of 54 subjects (n = 52).
*[3] t-test

Table 4. Percentage of anastomotic sites requiring any additional hemostatic procedure after protamine sulfate administration

	Matsudaito	Control	*P*-value*
Additional hemostatic procedures	19.4% (38/196)	55.6% (65/117)	<0.001
Re-application of Matsudaito	0.5% (1/196)		
Additional suturing	10.2% (20/196)	21.4% (25/117)	0.008
Fibrin products, conventional medical devices, or others	13.3% (26/196)	49.6% (58/117)	<0.001

* Fisher's exact test

Chest CT scans performed by postoperative hospital discharge as "postoperative examination of anastomotic sites" for safety evaluation showed no leakage of the contrast media, stenosis of ≥50% at anastomotic sites, or formation of pseudoaneurysm in either the Matsudaito or control group. Subjects were examined for any "signs and symptoms" based on overall findings from chest X-ray, patient interview, and medical examination. There was no significant between-group difference at either hospital discharge or Month 6. Symptoms in subjects with abnormal overall findings included pleural effusion, bilateral pleural effusion, pericardial effusion, thoracic cavity drainage, pericardial drainage, suspected calculus urinary, pyrexia, surgical operation-related atelectasis, a slight decrease in left lung permeability, mediastinitis, and pneumonia in the Matsudaito group; and pleural effusion, bilateral pleural effusion, pericardial effusion, dizziness, diarrhoea, left costophrenic angle dull, and left diaphragmatic eventration in the control group. "Pyrexia" continuously exceeding 38°C without a decreasing trend was reported in 1 subject (1.8%) in the Matsudaito group. The percentage of subjects having no abnormal change in "general laboratory tests (haematology and clinical chemistry)" was ≥87.3% in the Matsudaito group and ≥95.5% in the control group for all test parameters. At least 1 subject had an abnormal change in the following: differential white blood cell count - lymphocytes, differential white blood cell count - eosinophils, C-reactive protein (CRP), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine (a total of 7 test parameters) in the Matsudaito group; and hemoglobin level, hematocrit value, differential white blood cell count - monocytes, differential white blood cell count - eosinophils, and CRP (a total of 5 test parameters) in the control group.

The incidence of adverse events in the safety analysis population of 82 subjects (55 in the Matsudaito group, 27 in the control group) was 90.9% (50 of 55 subjects, 222 events) in the Matsudaito group and

88.9% (24 of 27 subjects, 95 events) in the control group. Table 5 shows adverse events with an incidence of ≥5%.

Table 5. Adverse events reported by ≥5% of subjects in either group

Adverse event	Matsudaito	Control
Pleural effusion	32.7% (18/55)	18.5% (5/27)
Pericardial effusion	14.5% (8/55)	3.7% (1/27)
Pyrexia	10.9% (6/55)	11.1% (3/27)
Increased CRP	10.9% (6/55)	11.1% (3/27)
Constipation	10.9% (6/55)	3.7% (1/27)
Sleeplessness	9.1% (5/55)	7.4% (2/27)
Increased ALT	7.3% (4/55)	0.0% (0/27)
Back pain	7.3% (4/55)	0.0% (0/27)
Wound pain	5.5% (3/55)	11.1% (3/27)
Atrial fibrillation	5.5% (3/55)	7.4% (2/27)
Mediastinitis	5.5% (3/55)	3.7% (1/27)
Pneumonia	5.5% (3/55)	3.7% (1/27)
Palpitations	5.5% (3/55)	3.7% (1/27)
Increased AST	5.5% (3/55)	0.0% (0/27)
Diarrhoea	5.5% (3/55)	0.0% (0/27)
Cardiac failure congestive	1.8% (1/55)	7.4% (2/27)
Pressure sore	1.8% (1/55)	7.4% (2/27)
Cerebral infarction	0.0% (0/55)	11.1% (3/27)
Vomiting	0.0% (0/55)	7.4% (2/27)

As shown in Table 6, adverse events for which a causal relationship to Matsudaito could not be ruled out occurred in 15 subjects (27.3%, 24 events). The events reported in ≥2 subjects included pleural effusion in 6 subjects (10.9%), pericardial effusion in 3 subjects (5.5%), and increased CRP and pyrexia in 2 subjects (3.6%) each.

Table 6. Number of subjects with adverse events for which a causal relationship to Matsudaito could not be ruled out

Severity / System Organ Class/event (n)		Mild	Moderate	Severe	Total (%)*	
Hepatic or biliary system disorders	Hepatic enzyme increased	0	1	0	1	1.8%
	Hepatic dysfunction	0	1	0	1	1.8%
Myocardial, endocardial, pericardial, or valvar disorders	Pericardial effusion	1	1	1	3	5.5%
	Delayed pericardial effusion	0	0	1	1	1.8%
	Pseudoaneurysm	0	0	1	1	1.8%
Vascular (non-cardiac) disorders	Old cerebral infarction	0	1	0	1	1.8%
Respiratory system disorders	Pleural effusion	1	1	4	6	10.9%
	Suspected pleurisy (pleural effusion)	0	0	1	1	1.8%
	Bilateral pleural effusion	1	0	0	1	1.8%
White blood cell or reticuloendothelial disorders	Increased eosinophils	1	0	0	1	1.8%
Platelet or hemorrhagic/blood coagulation disorders	High FDP-E	0	1	0	1	1.8%
	High fibrinogen	0	1	0	1	1.8%
General disorders	Pyrexia	1	1	0	2	3.6%
	Increased CRP	1	1	0	2	3.6%
Total		6	9	8	23	-

* The number of subjects (n = 55) in the Matsudaito group in the population that underwent aortic replacement (i.e., FAS) was used as the denominator in the calculation of the percentages.

Serious adverse events occurred in 24 subjects (45 events, 43.6%) in the Matsudaito group and 10 subjects (21 events, 37.0%) in the control group. Serious adverse events reported in ≥2 subjects included pleural effusion in 3 subjects, mediastinitis in 3 subjects, pericardial effusion in 3 subjects, and pneumonia in 3 subjects in the Matsudaito group, and cerebral infarction in 3 subjects in the

control group. Serious adverse events for which a causal relationship to Matsudaito could not be ruled out included pleural effusion in 2 subjects, suspected pleurisy (pleural effusion) in 1 subject, delayed pericardial effusion in 1 subject, and pseudoaneurysm in 1 subject (5 subjects in total). All of these events resolved or were resolving.

In this study, deaths occurred in 3 subjects in the Matsudaito group and 2 subjects in the control group (5 subjects in total). In addition, death in 1 subject in the Matsudaito group was reported at a follow-up examination after the end of postoperative follow-up period. Of the 3 subjects who died in the Matsudaito group, 1 subject experienced acute pulmonary oedema associated with anesthesia in jejunostomy conducted approximately 4 months after aortic arch replacement, and fell into sepsis, decreased blood pressure, and shock state, resulting in death. A causal relationship to Matsudaito was ruled out for this death. The second death case resulted from multi-organ failure. The subject experienced pneumonia approximately 1 month after aortic arch replacement involving median sternotomy, which led to dyspnea causing sternum disruption. Subsequent bacterial invasion into the mediastinum caused mediastinitis and pneumonia, resulting in multi-organ failure. A causal relationship to Matsudaito was ruled out for this death because the mediastinitis resulted most likely from infection in the mediastinum (including the artificial blood vessels), bone marrow, etc. caused by bacterial invasion from the wound surface of the sternum disruption, but not from infection that originated deep within the mediastinum at the anastomotic site where Matsudaito was applied. The third death case resulted from mediastinitis and hemorrhage from the graft anastomotic site. The mediastinitis was caused from infection at a disruption at the upper edge of the chest median wound, which occurred 2 weeks after aortic arch replacement. A causal relationship to Matsudaito was ruled out for this death because the infection originated from a place different from where Matsudaito was applied. The subject in the Matsudaito group who died after the end of postoperative follow-up period experienced mediastinitis 3 months after aortic arch replacement, resulting in death. A causal relationship to Matsudaito was ruled out for this death because autopsy of the subject revealed oesophagomediastinal fistula and this adverse event was most likely associated with oesophageal ulcer during the surgery.

No malfunction of Matsudaito was reported.

8.B. Outline of the review

PMDA's review mainly focused on the following points.

8.B.(1) Rationale for study design

In the clinical study, well-established institutional standard surgical procedures were used as the control to evaluate the hemostatic effect of Matsudaito at anastomotic sites immediately before and 15 minutes after heparin neutralizer, protamine sulfate administration during thoracic aorta replacement.

PMDA's view on this study design:

Currently, no hemostatic material has an established efficacy in the setting of impaired blood coagulation with heparin. The applicant aimed to develop a hemostatic material that is effective in that condition. In this clinical study, the efficacy of Matsudaito immediately before protamine sulfate

administration was selected as one of the primary endpoints. Since no hemostatic material has an established efficacy in the presence of heparin, no hemostatic material is used in clinical practice in most cases. Considering this situation, it is reasonable to use well-established institutional standard surgical procedures (e.g., surgical suturing) as a control.

Although no detailed information was provided regarding the standard surgical procedure conducted immediately before protamine sulfate administration in the control group at each study site, this would not affect the efficacy evaluation of Matsudaito profoundly for the following reasons: (1) No hemostatic material is used in clinical practice in most cases; (2) no hemostatic material has an established efficacy in the setting of impaired blood coagulation with heparin; (3) this investigational medical device was used to manage hemorrhage that could not be controlled by appropriate suturing; and (4) the use of a hemostatic material itself in the control group is a bias that negatively affects the efficacy evaluation of Matsudaito

8.B.(2) Efficacy of Matsudaito

PMDA asked the applicant to explain the mechanism that Matsudaito permanently maintains a hemostatic condition at the anastomotic site of artificial blood vessels, which usually does not heal.

The applicant's response:

There should be a slight gap at the anastomotic site of artificial blood vessels, where blood leakage can occur. Fibrins, platelets, and various blood cells in blood are attached to this gap and the intima of each artificial blood vessel. This leads to formation of clots and thin thrombus layers, preventing blood from leaking. These blood clots and thrombus layers are rich in red blood cells. The absorption of red blood cells increases fibrins and polymorphonuclear leukocytes, which become white thrombus-like tissue and then fibrinous thrombus-like tissue in 1 week. Into this tissue, fibroblasts infiltrate. At this point, almost permanent hemostasis is presumed to have been established. In 3 to 5 weeks, circulating endothelial cells start covering the lumen of the artificial blood vessels and eventually form a single cell layer.[5] Matsudaito used at the anastomotic site of artificial blood vessels blocks the blood flow from the gap at the anastomotic site by sealing the outside of the anastomotic site; this consequently promotes the formation of blood clots, resulting in prompt hemostasis. Matsudaito must remain firmly adhered to the vascular wall to maintain its hemostatic performance in the body. When Matsudaito was applied around the anastomotic site of blood vessels, it covered the anastomotic site as a gelatinous material at Month 3. At Month 16, the gelatinous material tightly covered the blood vessels [see Section "5.(3).1) Hemostatic experiment in a model of dog internal carotid artery anastomosis"]. A thinning test using rabbit abdominal aorta also demonstrated that Matsudaito was firmly adhered to the test site at Month 3 [see Section "5.(1).2) Biological safety"]. These findings indicate that Matsudaito remains firmly adhered to the anastomotic site of artificial blood vessels as well for at least 3 months.

PMDA's view on the efficacy of Matsudaito:

The results of the primary efficacy endpoints of "hemorrhage at each anastomotic site immediately before protamine sulfate administration" and "hemorrhage at each anastomotic site 15 minutes after protamine sulfate administration" showed that Matsudaito provided a significantly higher hemostatic effect (79.1% and 88.3%, respectively) than well-established institutional standard surgical procedures,

the control (38.5% and 60.7%, respectively). The percentage of subjects who required any additional hemostatic procedure, a secondary endpoint, was also significantly lower in the Matsudaito group (19.4%) than in the control group (55.6%). The efficacy of Matsudaito was thus demonstrated.

8.B.(3) Safety of Matsudaito

The Matsudaito group tended to have a higher incidence of pleural effusion (32.7% [18 of 55] of subjects), pericardial effusion (14.5% [8 of 55] of subjects), and mediastinitis (14.5% [3 of 55] of subjects) than the control group (18.5% [5 of 27] of subjects, 3.7% [1 of 27] of subjects, and 3.7% [1 of 27] of subjects, respectively). Of these adverse events, pleural effusion in 6 subjects and pericardial effusion in 3 subjects were related to Matsudaito. PMDA asked the applicant to explain the safety of Matsudaito for these events.

The applicant's explanation:

The incidence of pleural effusion after aorta replacement in a general clinical setting is unknown. A publication has reported that pleural effusion occurred in 45% to 63% of patients within 30 days after coronary artery bypass and/or valve replacement.[6] On the basis of this report, the incidence of pleural effusion in this clinical study is not particularly high. A medical institution in the US reported that the incidence of pericardial effusion requiring paracentesis after aortic arch replacement was 25%.[7] On the basis of this report, the incidence of pericardial effusion in this clinical study is not particularly high. The clinical study showed no significant difference in the incidence of pleural effusion or pericardial effusion, or the percentage of subjects requiring drainage between the Matsudaito and control groups. In addition, the dosage of Matsudaito did not significantly differ between subjects with and subjects without pleural or pericardial effusion, and between subjects requiring and subjects not requiring drainage. The incidence of pleural effusion or pericardial effusion, or the percentage of subjects requiring drainage did not depend on the dose of Matsudaito. In summary, Matsudaito was unlikely to have increased the risk of pleural or pericardial effusion.

The incidence of mediastinitis during thoracic aorta replacement was 6% according to a nationwide large-scale facility survey.[8] This is similar to the incidence of mediastinitis in the clinical study. A causal relationship to Matsudaito was ruled out for all cases of mediastinitis in the Matsudaito group in the clinical study. In summary, Matsudaito is unlikely to have increased the risk of mediastinitis.

The animal study of Matsudaito demonstrated the formation of a fibrous capsule and persistent foreign body reactions at the application site [see Section "5.(1).2) Biological safety"]. Since Matsudaito is not absorbed by the body, unlike the conventional hemostatic materials, it can contribute to persistent foreign body reactions and infection. PMDA asked the applicant to clarify a possible risk for this non-absorbable hemostatic material remaining in the body and then perform sufficient risk analysis based on the nonclinical and clinical studies of Matsudaito, and publications, etc. on non-absorbable hemostatic materials similar to Matsudaito.

The applicant's response:

Foreign body reactions depend on materials, extractables, and physical descriptions. Tissue irritation caused by Matsudaito resolved within 4 weeks with the gelatinous material covered with a fibrous

capsule. However, a phagocytic reaction persisted for a long period [see Section "5.(1).2) Biological safety"]). Similar findings (capsulation and macrophages) were observed with FocalSeal, which is approved by the US Food and Drug Administration (FDA) as a sealant for air leakage after pulmonary resection.[9] FocalSeal is a sealant mainly made of polyethylene glycol, and it polymerizes and forms into a gelatinous mass, which slowly decomposes in the living body and disappears in 600 days. FocalSeal is similar to the polymer of Matsudaito in that both are gelatinous substances having a polyethylene glycol structure. These materials are likely to disappear in a similar period of time. The foreign body reactions observed with Matsudaito appear to be common to hydrogels requiring a long period of time to decompose. The adverse effect of foreign body reactions on human health is probably negligible. However, because foreign body reactions occur frequently, a realistic risk mitigation actions should be taken to prevent them.

The risk of postoperative infection was also investigated. The incidence of postoperative infection in artificial blood vessel replacement is 1% to 6%.[10] It can be managed with antibiotics. In the first phase of postoperative infection, resident microorganisms attach to the surface of an implanted foreign body. This bacterial attachment profoundly differ depending on the property of implant materials. Resident microorganisms most easily adhere to intermediate hydrophobic materials.[11]-[13] The adhesion of *Staphylococcus epidermidis* and *Staphylococcus aureus*, resident microorganisms on the skin surface, to polyurethane central venous catheters and hydrogel-coated polyurethane catheters is significantly inhibited by hydrogel coating.[14] A study on the adhesion of *Staphylococcus epidermidis* to intraocular lens showed that the bacteria adhered most easily to the silicone surface, followed by heparinized polymethyl methacrylate (PMMA), hydrophobic acryl, fluorinated PMMA resin, and hydrogel in this order.[15] Since Matsudaito becomes a hydrogel substance through reaction with water at the application site, it is not expected to enhance bacterial adhesion to the skin surface, and is unlikely to cause postoperative infection.

PMDA's view on the safety of Matsudaito:
As explained by the applicant, the results of the clinical study show no significant increase in risk associated with the use of Matsudaito. However, the small sample size of the clinical study (55 in the Matsudaito group, 27 in the control group) has limitations in evaluating the safety of Matsudaito in terms of infection etc. Even if the clinical study has demonstrated the low relevance of Matsudaito to the safety risk, it is currently difficult to rule out the potential risk associated with the non-absorbable Matsudaito remaining in the body. In addition, adverse events, including pleural effusion, pericardial effusion, and mediastinitis, which are suspected to be related to Matsudaito remaining in the body, tended to occur more frequently in the Matsudaito group in the randomized, controlled clinical study. This should not be taken lightly considering that these adverse events can profoundly affect the prognosis of patients. For the safer use of Matsudaito, it is important to estimate this potential risk and to take appropriate risk mitigation actions. Relevant information on the risk for Matsudaito remaining in the body, risk mitigation actions, etc. should be fully provided to healthcare professionals. In addition, the risks of pleural effusion, pericardial effusion, and infections including mediastinitis should be focused on in the post-marketing surveillance.

8.B.(4) Directions for use of Matsudaito and risk mitigation actions

8.B.(4).1) Minimization of dosage

PMDA's view:

The applicant included the following statement in the "Warning" section of the proposed instructions for use to mitigate the risk of foreign body reactions and chronic infection.

> "Matsudaito should be used at a minimum required dose, and should not be used excessively or unnecessarily."

This risk minimization action by the applicant is appropriate. However, the proposed directions for use can be interpreted as recommending the circumferential application of Matsudaito. Because this may cause Matsudaito to remain on the surface other than bleeding sites, the information in the "Operation or usage method" section should be modified appropriately.

The applicant's response:

The illustrations labeled with "Circumferential application (example)" and "Partial application (example)" in the "Operation or usage method" section were removed. Instead, specific examples of the direct method and the transfer method are provided in this section. Other information was also revised. As for dosage, the condition "when the circumferential application of Matsudaito is required" was added.

PMDA accepted the applicant's response.

8.B.(4).2) Restricted use prior to heparin neutralization

PMDA's view:

In the clinical study, the Matsudaito group showed a higher hemostasis rate prior to heparin neutralization with protamine sulfate than the control group. However, the clinical usefulness (e.g., shortened operative duration and reduced blood loss) of hemostasis in the setting of impaired blood coagulation has not been demonstrated in patients, and therefore its clinical significance remains unclear. Compared with the application prior to neutralization, Matsudaito applied after heparin neutralization tended to have a higher hemostasis rate and required fewer additional hemostatic procedures. Further, fewer anastomotic sites require hemostasis after heparin neutralization, which reduces the dosage of Matsudaito. Based on the above, in order to minimize the dosage of Matsudaito, the application of Matsudaito should be limited to hemorrhage that is not controlled by surgical hemostasis in the setting of normal blood coagulation after heparin neutralization, as with conventional hemostatic materials. In some cases, however, hemostasis with Matsudaito prior to heparin neutralization can be inevitable at anastomotic sites, for example, distal to the aortic arch. PMDA asked the applicant to include a statement to the following effect in the "Warning" section of the instructions for use:

> The use of Matsudaito prior to heparin neutralization should be restricted to cases where full surgical hemostatic procedures alone are very unlikely to provide full hemostasis and therefore hemostasis with Matsudaito prior to heparin neutralization is required.

The applicant's response:
In thoracic aorta replacement or branching artery arch replacement, implementing hemostatic procedures after heparin neutralization may be difficult depending on sites and cases. The following statement will be added to the "Warning" section of the instructions for use:

> "Matsudaito should not be used in patients with impaired blood coagulation prior to heparin neutralization unless its use is absolutely necessary, for example, when hepatic procedures after heparin neutralization are difficult to implement."

PMDA accepted the applicant's response.

8.B.(4).3) Additional hemostatic procedures

In the clinical study, 38 anastomotic sites required an additional hemostatic procedure because of incomplete hemostasis with Matsudaito. Of them, 20 anastomotic sites received additional suture and 1 site received Matsudaito. PMDA asked the applicant to clarify additional hemostatic procedures to be taken when the initial use of Matsudaito fails to provide hemostasis and the appropriateness of using Matsudaito for this purpose.

The applicant's response:
Hemorrhage from the anastomotic site of artificial blood vessels needs to be stopped or reduced by sutures as much as practical. The protocol of the clinical study required the surgeons to perform sufficient suturing prior to the initial use of Matsudaito. Since the protocol also required application of Matsudaito prior to protamine sulfate administration, some subjects were found to require additional suturing after heparin neutralization with protamine sulfate. As a result, many subjects ended up receiving additional suturing as an additional hemostatic procedure. If the initial use of Matsudaito fails to provide complete hemostasis despite prior sufficient suturing, the additional use of Matsudaito is expected to provide complete hemostasis. Prior to the use of Matsudaito as an additional hemostatic procedure, patients should be observed for any hemorrhage. If suturing is appropriate for hemostasis, additional sutures should be inserted. When suturing is not expected to provide hemostasis, the additional use of Matsudaito is required. If there is a gap between the bleeding site and the sealant coating from the initial application, additionally applied Matsudaito prevents the bleeding site from adhering tightly to the sealant and does not help hemostasis. In this case, the initial sealant coating around the bleeding site should be removed without damaging the outer membrane of the blood vessels, and then a minimum required dose of Matsudaito should be applied to the area closest to the bleeding site.

PMDA accepted the applicant's response and concluded that the necessity of removing the solidified coating of Matsudaito should be included in the instructions for use as a precaution.

8.B.(4).4) Use of artificial blood vessels made of low permeable materials

Since Matsudaito is non-absorbable, its use at anastomotic sites of blood vessels made of low permeable materials may increase the potential risk of infection. Because infection will make curative treatment difficult, PMDA asked the applicant to raise caution that the risks and benefits of Matsudaito should be discussed carefully before the use of the product.

The applicant responded that a relevant precautionary statement would be included in the "Warning" section of the instructions for use. PMDA accepted the applicant's response.

8.B.(5) Clinical positioning of Matsudaito

The applicant's explanation:

The applicant developed Matsudaito as a synthetic hemostatic material made of raw materials not derived from humans or animals (free from the risk of viral infection) that (a) ensures hemostasis at vascular anastomotic sites even in the setting of impaired blood coagulation, where hemostasis is difficult to achieve with conventional hemostatic materials, and (b) has an enough tissue adhesiveness and flexibility to tolerate the blood pressure at anastomotic sites. The results of the nonclinical and clinical studies demonstrated that Matsudaito conformed to its initially defined purposes.

PMDA's view on the clinical positioning of Matsudaito:

The clinical study showed the significantly higher hemostasis rate with Matsudaito than with the control procedures both immediately after and 15 minutes after protamine sulfate administration, the primary endpoints. However, the clinical usefulness (e.g., shortened operative duration and reduced blood loss) of hemostasis in the setting of impaired blood coagulation prior to heparin neutralization has not been demonstrated in patients, and therefore the clinical significance of using Matsudaito prior to heparin neutralization remains unclear. In addition, since Matsudaito is not absorbed by the body, unlike the conventional hemostatic materials, it may cause persistent foreign body reactions and infection; and the clinical study suggested a possible increase in the risk of infection. Based on the above, in order to minimize the dose of Matsudaito, the application of Matsudaito should be limited in principle to hemorrhage that is not controlled by surgical hemostasis in the setting of normal blood coagulation after heparin neutralization, as with conventional hemostatic materials. For the following reasons, however, making Matsudaito available in the clinical practice is clinically meaningful:

(a) Hemostasis with Matsudaito prior to heparin neutralization can be inevitable at anastomotic sites, for example, distal to the aortic arch.
(b) Hemostasis at anastomotic sites of artificial blood vessels using normal hemostatic procedures can be difficult even after heparin neutralization.

8.B.(6) Intended use and indication of Matsudaito

PMDA's view:

The proposed intended use and indication in the present application are "Hemostasis at the site of vascular anastomosis (between blood vessel and blood vessel, between blood vessel and artificial blood vessel, or between artificial blood vessel and artificial blood vessel)." This means that Matsudaito can be used at any site of vascular anastomosis. However, even if healthcare professionals are instructed to use Matsudaito at a minimum required dose, the potential risk associated with Matsudaito, a non-absorbable hemostatic material, remaining in the body will not be profoundly reduced. It is also difficult to estimate the significance of the risk. Considering its risk-benefit balance, currently, it is best to limit the use of Matsudaito to diseases that will benefit most from Matsudaito. The efficacy of Matsudaito has been shown in the submitted clinical study. The difficulty of hemostasis in those diseases and the effect of using Matsudaito on the patient's prognosis should also

be taken into consideration. Taken together, PMDA asked the applicant to change the proposed intended use and indication of Matsudaito as shown below.

Intended Use and Indication
Auxiliary hemostasis at the site of artificial vascular anastomosis associated with thoracic aorta replacement or branching artery arch replacement in which hemostasis cannot be achieved by usual surgical procedures including ligation

The applicant responded that the proposed intended use and indication would be changed accordingly. PMDA accepted the applicant's response.

8.B.(7) Use in children
Pleural effusion or pericardial effusion profoundly affects the hemodynamics, respiration, and general condition of children. In addition, Matsudaito, a foreign body, may adversely affect the surrounding tissue in the process of children's growth. Since the safety of Matsudaito in children has not been established, PMDA asked the applicant to explain their view on the pediatric use of Matsudaito.

The applicant's response:
Thoracic aorta replacement or branching artery arch replacement poses a substantial risk to children because their vascular diameter becomes bigger as they grow. These replacement surgeries are therefore rarely conducted in children. Currently, the relationship between Matsudaito and pleural effusion or pericardial effusion is unclear. Careful consideration is needed before using Matsudaito in children.

PMDA's view:
The proposed instructions for use include the precaution that Matsudaito should be used in children only when the therapeutic benefits outweigh the possible risks associated with treatment because its safety in children has not been established. Thus, there is currently no particular problem with the applicant's view and actions.

8.B.(8) Post-marketing surveillance etc.
PMDA's view:
The clinical study suggested the potential risks of infection and inflammation associated with the placement of this non-absorbable material. Very limited safety information is available from the study because only 55 patients were treated with Matsudaito. Matsudaito is the first non-absorbable hemostatic material in Japan, and the long-term safety of implanted Matsudaito has not been demonstrated. For these reasons, it is necessary to focus on the incidence, severity, causality of adverse events of special interest (pleural effusion, pericardial effusion, and mediastinitis), infection, and pyrexia in the post-marketing surveillance, as well as to collect information regarding the long-term safety in more patients. The dosage and timing of use (before or after protamine sulfate administration) of Matsudaito, type of artificial blood vessels used, additional hemostatic procedures (yes/no; details of the procedure if yes), etc. should also be investigated in this surveillance. PMDA asked the applicant to submit the outline of the post-marketing surveillance plan.

The applicant's response:
The planned surveillance period is 3 years, with the planned sample size of 500 patients. Appropriate surveillance items will be specified.

PMDA considered that although the details of the post-marketing surveillance plan needed to be further reviewed, the outline of the proposed post-marketing surveillance plan was largely appropriate, and accepted the applicant's response.

8.B.(9) Comments at Expert Discussion

The following comments were raised from expert advisors at the Expert Discussion:

(1) The efficacy of Matsudaito has been demonstrated. As explained by PMDA, however, the potential risk associated with Matsudaito cannot fully be ruled out. When bacteria enter the gap between an artificial blood vessel and non-absorbable Matsudaito, antibiotics are less likely to enter the gap and the metabolism at the gap decreases. The gap may become a focus of infection. It is important to take risk mitigation actions, such as not using Matsudaito over a large area on the surface of an artificial blood vessel.

(2) The clinical study showed the high incidence of pleural effusion, pericardial effusion, mediastinitis, etc. Currently, however, the causal relationship between these events and Matsudaito is unknown because of the limited sample size of the study. This information should be included in the instructions for use. These events should be carefully monitored in the post-marketing surveillance, etc.

The expert advisors also commented that hemostatic materials for vascular anastomosis, including Matsudaito and conventional products, do not replace vascular suturing and are just auxiliary hemostatic methods to treat exudative hemorrhage, therefore, Matsudaito should be used after heparin neutralization following sufficient vascular suturing. On the other hand, the expert advisors commented that the use of Matsudaito prior to intravenous injection of protamine should also be permitted depending on anastomotic sites because there are some areas that are not easily accessible (e.g., distal anastomosis during aortic arch replacement) at the time of intravenous injection of protamine (i.e., at the end of extracorporeal circulation after the completion of all procedures for anastomosis of artificial blood vessels).

For the intended use and indication of Matsudaito, the expert advisors commented that Matsudaito should not be used casually at anastomotic sites of blood vessels, although there was no objection to its use at anastomotic sites between an artificial blood vessel and a blood vessel or between artificial blood vessels.

The PMDA's views presented in Sections 8.B.(1) to 8.B.(8) based on the comments at the Expert Discussion, were supported by expert advisors.

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

Results of document-based compliance inspection

The new medical device application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of Paragraph 5, Article 14 of the Pharmaceutical Affairs Act. On the basis of the inspection and assessment, no particular problems were noted, and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

Results of the QMS document-based and on-site inspection

The new medical device application data were subjected to a QMS document-based and on-site inspection in accordance with the provisions of Paragraph 6, Article 14 of the Pharmaceutical Affairs Act. PMDA concluded that there were no particular problems.

V. Overall Evaluation

Matsudaito is a non-absorbable hemostatic material used for hemostasis at vascular anastomotic sites. The PMDA's review on Matsudaito focused on (a) the efficacy of Matsudaito, (b) the risk for the non-absorbable hemostatic material, and (c) the proper use of Matsudaito after the market launch. PMDA's conclusions based on discussions with the expert advisors, are as shown below.

(a) In the submitted clinical study, the results of the primary efficacy endpoints ([a] hemorrhage at each anastomotic site immediately before protamine sulfate administration and [b] hemorrhage at each anastomotic site 15 minutes after protamine sulfate administration) showed that the hemostatic effect was significantly higher in the Matsudaito group ([a] 79.1% and [b] 88.3%) than in the control group ([a] 38.5% and [b] 60.7%) (well-established standard surgical procedures at each study site were used as the control). The percentage of subjects requiring any additional hemostatic procedure, a secondary endpoint, was also significantly lower in the Matsudaito group (19.4%) than in the control group (55.6%). These results demonstrated the efficacy of Matsudaito.

(b) Matsudaito, which is not absorbed in the body, may be associated with a higher risk of inflammation or infection than conventional absorbable hemostatic materials. In fact, the animal tests showed persistent foreign body reactions at the application sites. Although the clinical study showed no significant increase in risk associated with the use of Matsudaito, the small sample size of the clinical study (55 in the Matsudaito group, 27 in the control group) has limitations in evaluating the safety Matsudaito, including infection. It is currently difficult to rule out the potential risk associated with this non-absorbable hemostatic Matsudaito remaining in the body even if the clinical study has shown the low contribution of Matsudaito to the risk. In addition, adverse events, including pleural effusion, pericardial effusion, and mediastinitis, which are suspected to be related to Matsudaito remaining in the body, tended to occur more frequently in the Matsudaito group. This should not be taken lightly because these adverse events can profoundly affect the prognosis of patients. For this reason, the relationship between Matsudaito

and the risk associated with the non-absorbability of Matsudaito should be discussed based on the results of the post-marketing surveillance.

(c) Matsudaito is associated with the possible risk of inflammation or infection that is not expected to occur with conventional absorbable hemostatic materials. The results of the submitted clinical study alone are not sufficient to strongly rule out the relationship between Matsudaito and these risks. The use of Matsudaito should therefore be limited to diseases that (a) will clinically benefit from Matsudaito and (b) obtained a high hemostatic performance of Matsudaito with a certain level of safety in the clinical study. In conclusion, the intended use of Matsudaito should be "Auxiliary hemostasis at the site of artificial vascular anastomosis associated with thoracic aorta replacement or branching artery arch replacement in which hemostasis cannot be achieved by usual surgical procedures including ligation." For the safe and proper use of Matsudaito, it is important to understand the potential risks associated with non-absorbable materials and to minimize the dose of Matsudaito. This information on these risks should be included in the instructions for use to raise caution. In addition, healthcare professionals should be fully informed about the potential risks of inflammation, infection, etc. attributable to this non-absorbable hemostatic Matsudaito remaining in the body, risk mitigation actions, etc.

Matsudaito was developed as a hemostatic material that can be used prior to heparin neutralization with protamine sulfate. For the reasons presented below, however, the application of Matsudaito should be limited to hemorrhage that is not controlled by surgical hemostasis in the setting of normal blood coagulation after heparin neutralization, as with conventional hemostatic materials, in order to minimize the dose of Matsudaito:

(1) The clinical study showed the significantly higher hemostasis rate with Matsudaito than with the control procedures. However, the clinical usefulness (e.g., shortened operative duration and reduced blood loss) of starting the hemostatic procedure prior to heparin neutralization has not been demonstrated in patients.
(2) The hemostasis rate with Matsudaito tends to be higher after heparin neutralization, with a fewer number of additional hemostatic procedures, than prior to neutralization.
(3) Fewer anastomotic sites require hemostasis after heparin neutralization, which reduces the dose of Matsudaito.

In some cases, however, hemostasis with Matsudaito prior to heparin neutralization can be inevitable at anastomotic sites, for example, distal to the aortic arch. The use of Matsudaito prior to heparin neutralization should be restricted to cases where full surgical hemostatic procedures alone are very unlikely to provide full hemostasis and therefore hemostasis with Matsudaito prior to heparin neutralization is required.

As a result of its review, PMDA has concluded that Matsudaito may be approved for the intended use shown below.

Intended Use and Indication

Auxiliary hemostasis at the site of artificial vascular anastomosis associated with thoracic aorta replacement or branching artery arch replacement in which hemostasis cannot be achieved by usual surgical procedures including ligation

Since this product is a medical device with a new performance, the re-examination period should be 3 years. The product is not classified as a biological product or a specified biological product.

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

VI. References

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