June 12, 2023
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Synthetic myocardial patch
Brand Name	Synfolium
Applicant	TEIJIN MEDICAL TECHNOLOGIES CO., LTD.
Date of Application	January 23, 2023 (Application for marketing approval)

Results of Deliberation

In its meeting held on June 12, 2023, 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 is designated as a medical device subject to a use-results survey, and the use-results survey period should be 7 years. The product is not classified as a biological product or a specified biological product.

The product should be approved with the following conditions.

Approval Conditions

1. The applicant is required to submit the results of interannual analyses of long-term prognosis data from participants in the clinical study for marketing approval to the Pharmaceuticals and Medical Devices Agency and to take appropriate measures as necessary.
2. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product in the aorta, in accordance with the proper use guidelines prepared in cooperation with the relevant academic societies, and to submit to the Pharmaceuticals and Medical Devices Agency the results of interannual analyses of long-term prognosis while taking appropriate measures as necessary.

Review Report

May 17, 2023

Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Synthetic myocardial patch
Brand Name	Synfolium
Applicant	TEIJIN MEDICAL TECHNOLOGIES CO., LTD.
Date of Application	January 23, 2023
Items Warranting Special Mention	SAKIGAKE designation device (SAKIGAKE Device Designation No.1 of 2017 [29 ki]) SAKIGAKE comprehensive assessment consultation was conducted.
Reviewing Office	Office of Medical Devices I

Review Results

May 17, 2023

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Synthetic myocardial patch
Brand Name	Synfolium
Applicant	TEIJIN MEDICAL TECHNOLOGIES CO., LTD.
Date of Application	January 23, 2023

Results of Review

"Synfolium" is a synthetic myocardial patch used for correction of blood flow, securing blood flow paths, and generation/reconstruction of surrounding tissues in congenital cardiac surgery. Synfolium has an integrated structure in which a knitted fabric composed of a biodegradable synthetic polymer (poly-L-lactic acid [PLLA] yarn) and a non-biodegradable synthetic polymer (polyethylene terephthalate [PET] yarn) is coated with a crosslinked gelatin (gelatin and glycerin) membrane. On the basis of the development concept, Synfolium was designed in a manner that after biodegradable PLLA yarns are degraded and absorbed following implantation, the remaining non-biodegradable PET yarns stretch to accommodate tissue growth while maintaining the strength of the patient's regenerated tissue.

The applicant submitted non-clinical data supporting the biological safety, stability, durability, and performance. There were no particular problems with the data.

The applicant submitted clinical data on patients with congenital heart diseases from Study OFT-G1-301 conducted at 6 study centers in Japan. The point estimate for the primary endpoint "the surgical success rate in the year following surgery" was 100% (34 of 34 subjects), with a 90% confidence interval (CI) of 91.6% to 100.0%. The lower limit 91.6% exceeded the prescribed threshold of [redacted]%, demonstrating the efficacy of Synfolium as defined in the protocol.

In Study OFT-G1-301, no patients underwent implantation of Synfolium in the aorta, the artery that must be able to withstand the greatest blood pressure. However, it was decided not to exclude the aorta from the indication of Synfolium because there were no adverse events that could raise concerns in subjects undergoing implantation on the vessel wall subjected to relatively high blood

pressure, and findings including tissue regeneration have been observed in Synfolium implanted in the canine descending aortic wall. However, it was decided that the institutions that can use Synfolium in the aorta after the product launch should be limited until data accrued from the use-results survey over a specified period are evaluated, and thereafter, institutions that can use Synfolium in the aorta should be gradually added in stages.

Because of the difficulty of performing long-term evaluation in clinical trials, the clinical evaluation data have not been sufficiently assessed in relation to the development concepts of Synfolium, i.e., extensibility to accommodate growth, reduction in calcification and other material deterioration, and prevention of stenosis caused by intima hyperplasia, which are advantages unique to Synfolium. However, non-clinical studies have shown findings such as extensibility of Synfolium, degradation behavior of PLLA, and tissue regeneration in the implanted areas; furthermore, no adverse events of concern were reported in the clinical studies; therefore, Synfolium is expected to demonstrate these advantages in the future. It is considered important to gather not only data from the use-results survey but also longer-term clinical data in cooperation with the relevant academic societies, and provide information to the healthcare professionals regarding the advantages unique to Synfolium.

As a result of its review, PMDA has concluded that Synfolium may be approved for the intended use shown below, with the following approval conditions, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

Synfolium is used for correction of blood flow, securing blood flow paths, and generation/reconstruction of surrounding tissues in congenital cardiac surgery.

Approval Conditions

1. The applicant is required to submit the results of interannual analyses of long-term prognosis data from participants in the clinical study for marketing approval to the Pharmaceuticals and Medical Devices Agency and to take appropriate measures as necessary.
2. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product in the aorta, in accordance with the proper use guidelines prepared in cooperation with the relevant academic societies, and to submit to the Pharmaceuticals and Medical Devices Agency the results of interannual analyses of long-term prognosis while taking appropriate measures as necessary.

Review Report

May 17, 2023

Product for Review

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Synthetic myocardial patch
Brand Name	Synfolium
Applicant	TEIJIN MEDICAL TECHNOLOGIES CO., LTD.
Date of Application	January 23, 2023
Proposed Intended Use	Synfolium is used for correction of blood flow, securing blood flow paths, and generation/reconstruction of surrounding tissues in cardiovascular surgery. The patient's tissue is regenerated at the implanted site, leading to reduction in deterioration such as calcification.
Items Warranting Special Mention	SAKIGAKE designation device (SAKIGAKE Device Designation No.1 of 2017 [29 ki]) SAKIGAKE comprehensive assessment consultation was conducted.

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List of Abbreviations

ADME	Absorption Distribution Metabolism Excretion
AMED	Japan Agency for Medical Research and Development
BSA	Body Surface Area
CT	Computed Tomography
ECG	Electrocardiogram
FAS	Full Analysis Set
GA	Glutaraldehyde
DMC	Data Monitoring Committee
MD	Machine Direction
FIH	First in Human
HE	Hematoxylin Eosin
ISO	International Organization for Standardization
FS	Fractional shortening
MAPCA	Major Aortopulmonary Collateral Artery
LQT	Long QT Syndrome
PBS	Phosphate Buffered Saline
PET	Polyethylene Terephthalate
PLLA	Poly-L-Lactic Acid
PPS	Per Protocol Set
PTFE	Polytetrafluoroethylene
QOL	Quality of Life
TD	Transverse Direction

I. Product Overview

"Synfolium" is a synthetic myocardial patch used for correction of blood flow, securing blood flow paths, and generation/reconstruction of surrounding tissues in congenital cardiac surgery. Synfolium has an integrated structure in which a knitted fabric composed of a biodegradable synthetic polymer (poly-L-lactic acid [PLLA] yarn) and a non-biodegradable synthetic polymer (polyethylene terephthalate [PET] yarn) is coated with a crosslinked gelatin (gelatin and glycerin) membrane (Figure 1). Concurrently with the degradation and bioabsorption process of PLLA yarn, regenerative tissue permeates the patch and grows, leading to formation of new vessel-like tissue containing vasa vasorum. The PET yarn is designed to stretch to accommodate tissue growth after PLLA degradation, while retaining the strength of the patient's regenerated tissue.

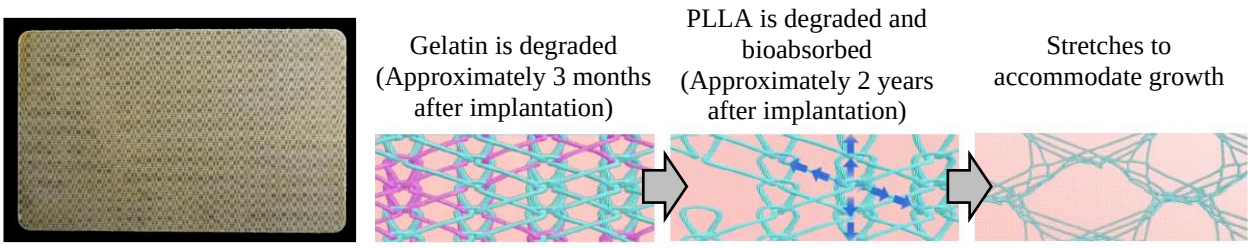

Figure 1. Appearance of Synfolium and schematic diagrams for absorption and stretching processes

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

The data submitted in this 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 Synfolium declared that they did not fall under the Item 5 of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Approximately 1% of infants born in Japan have a congenital heart disease,[1] and approximately 9,000 surgical repairs are performed annually.[2] Congenital heart diseases are malformations present in 3 segments, the atria, ventricles, and the great arteries, abnormal positional relationships, and abnormal intersegmental connections. In some patients, more than 1 defect is involved. Approximately 160 types of procedures are used in a range of age groups, from newborns to

adults, to treat approximately 200 diseases.[3] Some patients have 2 or more disease types, and it may be difficult to save lives in such complex cases.

Many patients with congenital heart disease undergo surgery using prosthetic material during childhood to correct blood flow and secure blood flow paths. Prosthetic materials are used to repair defects such as those affecting the septum and vessel wall of the heart. Prosthetic materials that have been approved in Japan as medical devices (hereinafter referred to as the "conventional patches") include glutaraldehyde (GA)-treated "Bovine Pericardial Patch" (Approval No. 22200BZX00841000) and PTFE patch, "Gore-Tex® EPTFE Patch II (cardiovascular patch)" (Approval No. 16000BZY00180000). Recently, reconstruction with autologous tissue has become widespread and autologous pericardium has been frequently used.

In recent years, surgical outcomes have been improving with the advancement of medical technology, and patients with congenital heart disease now live longer. Approximately 90% of children with congenital heart disease survive into adulthood;[1] however, there are long-term problems arising from implanted materials, namely, deterioration/calcification, development of complications such as vessel restenosis, and sequela. Various factors are involved in these problems: deformation associated with growth at the reconstruction site or surgery site, relative growth disturbance, tissue growth or aneurysmal change due to abnormal blood flow such as swirling, artificial materials becoming stiff, degenerating or bulging, and secondary degeneration due to infection. Modern high-precision diagnostic technology allows diagnosis of minor persistent diseases and sequela, although not all of them require treatment. However, in some cases, reoperation or catheterization is indicated, leading to substantial physical and economic burdens being imposed on patients and their families.

In pediatric patients, in particular, morphological changes may occur even if their own tissue is used. This is because of disparity in the balance between the growth in the direct, invasive reconstruction site and that in the non-invasive site. None of the conventional patches have the extensibility able to accommodate the growth of the heart and vessels, which causes problems that are common to all these patches, such as vessel restenosis in the long term after initial repair.

To examine the clinical needs for conventional treatment methods and the performance required for Synfolium, the applicant conducted a questionnaire survey[4] with cardiovascular surgeons and pediatric cardiologists in 2020 with the cooperation of Japanese Society of Pediatric Cardiology and Cardiac Surgery, regarding the types of patches used for extensive reconstruction of the right ventricular outflow tract to the pulmonary artery region, and the frequency and causes of reintervention (reoperation and catheter intervention). Data were obtained from 31 responders.

The results showed that Gore-Tex EPTFE Patch II accounted for 60% of all uses by frequency, autologous pericardium 30%, and Bovine Pericardial Patch 10%, with a 3-year freedom from reintervention of 80.2%. The top 3 causes of reintervention, namely, “material deterioration (including calcification),” “stenosis due to intima hyperplasia,” and “non-extensibility of the patch,” were common regardless of the type of patch used, and these 3 causes accounted for approximately 80% of reinterventions.

The results indicated that patches needed in the clinical practice must have the following characteristics: materials used are less prone to deterioration; the vessel function comparable to that of living blood vessels is restored without causing intima hyperplasia; and ability to stretch as tissue grows. However, it would take in the order of 10 years to evaluate the development concepts, e.g., reduction in restenosis, calcification, deterioration, etc., freedom from reoperation due to device-patient size mismatch associated with growth in the long term after initial repair; therefore, it was decided that development should proceed first by demonstrating the equivalence with conventional patches.

From FY2014, Synfolium was developed jointly with Osaka Medical College (currently Osaka Medical and Pharmaceutical University), TEIJIN LIMITED, TEIJIN MEDICAL TECHNOLOGIES CO., LTD., and Fukui Tateami Co., Ltd., supported by the Ministry of Economy and Trade and Industry and the Commercialization Promotion Project for Medical-engineering Collaboration supported by the Japan Agency for Medical Research and Development (AMED). The intended population comprises patients with serious congenital heart disease that are likely to require multiple surgeries during early childhood. As Synfolium has characteristics based on principles different from those of conventional patches and is expected to be highly innovative, the use of Synfolium may result in avoiding reoperations that would be otherwise be required due to the patient’s growth. For these reasons, Synfolium was designated on March 27, 2018 as a SAKIGAKE product, an innovative and world-leading product to be developed early in Japan under the SAKIGAKE Designation System for Medical Devices sponsored by the Ministry of Health, Labour and Welfare (MHLW).

1.A.(2) Use in foreign countries

Synfolium is developed in Japan and has not been used in other countries.

2. Design and Development

2.(1) Performance and safety specifications

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

The proposed performance specifications for Synfolium include tensile strength and water permeability. The proposed safety specifications include bacterial endotoxins, biological safety, and ethylene oxide sterilization residuals.

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

Synfolium is required to have sufficient strength and flexibility as a patch for a specific time period and be free from problems such as blood leak and rupture during the process in which the biodegradable component is absorbed. Accordingly, PMDA asked the applicant to include degradation characteristics of the biodegradable component in the performance and safety specifications. PMDA also asked the applicant to include [redacted] strength and pinhole leak in the performance and safety specifications to assure the strength and other properties of the patch.

The applicant's response:

The specifications for PLLA degradability characteristics include [redacted]-averaged molecular weight of early PLLA and [redacted] strength at [redacted] and [redacted] months after [redacted] in [redacted]. In addition, [redacted] strength and pinhole leak are included in the specifications to assure the strength of the patch.

PMDA considers that the applicant's view and response are appropriate. In addition, PMDA reviewed performance and safety specification data for the appropriateness of specifications and concluded that there were no particular problems.

2.(2) Biological safety

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

The applicant submitted the results of a biological safety study of Synfolium conducted in accordance with the "Amendment of Basic Principles of Biological Safety Evaluation Required for Application for Approval to Market Medical Devices" (PSEHB/MDED Notification No.0106-1, dated January 6, 2020).

To investigate biological safety, the applicant conducted tests on cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, genotoxicity (reverse mutation assay and chromosomal aberration assay), pyrogen, implantation, hemocompatibility, and juvenile animal systemic toxicity. The submitted test results showed no problems except for a weak cytotoxic effect identified by the cytotoxicity study.

The known information on the raw materials and results of the long-term implantation test indicated that there are no problems with the absorption, distribution, metabolism, and excretion (ADME) of the bioabsorbable materials, i.e., gelatin and PLLA.

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

The results of the cytotoxicity test indicated that Synfolium was weakly cytotoxic. The applicant considered the results were attributable to [redacted], which suppresses cell proliferation. PMDA asked the applicant to discuss the safety of the use of Synfolium in neonates.

The applicant's response:

Data have demonstrated that [redacted] suppresses cell proliferation in cell culture at a concentration of [redacted] v/v%,[5] which is calculated to be [redacted] mg/mL based on the specific gravity of [redacted] ([redacted]).[6] Under the test conditions, the concentration of [redacted] dissolved into the cell culture was [redacted] mg/mL, which is a concentration that suppresses cell proliferation, and this resulted in the colony forming capability being reduced by >30%. Conversely, no abnormalities in colony forming capability were noted at [redacted] mg/mL, the concentration of [redacted] in 50% extract. The above findings indicated that the "weakly cytotoxic" are attributable to [redacted] released into the medium extract.

If a [redacted]-cm oval patch of Synfolium is used for a neonates weighing 3 kg, the estimated blood [redacted] concentration is [redacted] mg/mL, which is unlikely to cause cell death. Additionally, given that no findings in the implantation study indicated tissue injury, and that no tissue injury or proinflammatory characteristics were indicated in the intracutaneous reactivity study, it is considered that Synfolium is unlikely to cause chronic tissue injury.

PMDA comprehensively reviewed the data on biological safety and concluded that there were no particular problems.

2.(3) Stability and durability

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

All the raw materials used in Synfolium are used in medical devices such as artificial blood vessels. The applicant therefore submitted a self-declaration in accordance with the "Handling of stability studies related to the determination of the shelf life in the application for marketing approval (certification) of medical devices," PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012.

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

PMDA reviewed the data on stability and durability and concluded that there were no particular problems.

2.(4) Performance

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

To support the performance of Synfolium, the applicant submitted data from the tests on tensile strength, suture retention strength, [redacted] strength, water permeability, pinhole leak, stretching, *in vitro* degradation, implantation in an animal vessel wall, long-term implantation in an animal vessel wall ([redacted] years, [redacted] years), comparison of long-term implantation in an animal vessel wall, and long-term implantation in an animal vessel wall ([redacted] years).

The evaluation of the development concepts (stretching, *in vitro* degradation, and animal studies) are summarized below:

Stretching study

The knitted portion of Synfolium was immersed in [redacted] mol/L [redacted], [redacted] at [redacted]°C for [redacted] hours to specifically degrade PLLA. With this sample, the study was conducted using [redacted]. Because the heart grows with somatic growth, the annulus diameter of the heart valve roughly doubles in size from 2 to 3 month after birth to 20 years of age,[7] and the vessels connected to the heart valve also grow in a similar manner.[8] In this study, acceptance criteria for stretching by [redacted] in both directions, machine direction (MD) and transverse direction (TD) were selected. The results of measurement showed that [redacted] in both MD and TD, and the acceptance criteria were met.

***In vitro* degradability test**

The test was conducted to evaluate if Synfolium maintains sufficient strength until [redacted] after implantation. [redacted], the samples were stored at [redacted]°C/[redacted] rpm [redacted], and the molecular weight of PLLA was measured at [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] months later to check the [redacted] strength and progress of degradation. The samples stored for [redacted] months exceeded the specifications ([redacted]) for both directions (MD and TD), selected based on [redacted] strength specifications. [redacted] strength decreased over time, and [redacted] at ≥[redacted] months of storage. [redacted]. The molecular weight of PLLA decreased with storage period, indicating decline in [redacted] strength with the progress of degradation.

Animal studies

Table 1 shows a summary of each animal study. The applicant submitted data from studies of implantation in the animal vessel wall in beagles (N = [redacted]) and minipigs (N = [redacted]) as reference data.

Table 1. Summary of animal studies

Name of study Device tested (number of animals)	Details of evaluation
Study of implantation in animal vessel wall Test device: Synfolium (N = [redacted] for [redacted] weeks; N = [redacted] for [redacted] weeks) Control device: Gore-Tex EPTFE Patch II (N = [redacted] for [redacted] weeks)	An oval shaped patch (1 cm × 2 cm) of the test device or the control device was implanted at the defect site of the descending thoracic aorta of beagles. The devices were evaluated at [redacted] weeks and [redacted] weeks (test device) and [redacted] weeks (control device) for the items shown below based on data including necropsy findings. **Tissue regeneration** • Evaluation by histological examination of tissue regeneration status at the implanted site • Observation by gross examination of areas around the implanted site and blood vessel lumen surface for any anomaly • Gross and histological evaluation of the kidney and other organ/tissue for any infarct change caused by blood clots breaking loose to evaluate stability on the luminal surface of the implanted areas **Presence of morphological anomalies** • Confirmation by angiography of findings such as blood flow and rupture at the implanted site • Measurement of vessel diameters, minimum, maximum, and mean diameters at the implanted site, and at the head and bottom ends • Calculation of aneurysmal change rate and stenotic rate **General condition** Clinical signs, body weight, hematology, and blood biochemistry
Study of long-term implantation in animal vessel wall ([redacted] years, [redacted] years) Test device: prototype using non-medical PLLA (N = [redacted] for [redacted] years, N = [redacted] for [redacted] years)	An oval shaped patch (1 cm × 2 cm) of the test device was implanted at the defect site of the descending thoracic aorta of beagles. The devices were evaluated for the items shown below at [redacted] and [redacted] years. **Tissue regeneration** • Observation by gross examination of appearance at the implanted site • Evaluation by histological examination of tissue regeneration status at the implanted site **Mechanical evaluation** Tensile strength, stretching studies, and PLLA molecular weight
Comparison study of long-term implantation in animal vessel wall Test device: Synfolium (N = [redacted] for [redacted] years) Control devices: Gore-Tex EPTFE Patch II (N = [redacted] for [redacted] years), Bovine Pericardial Patch (N = [redacted] for [redacted] years)	An oval shaped patch (1 cm × 2 cm) of the test device or the control device was implanted at the defect site of the descending thoracic aorta of beagles. The devices were evaluated at [redacted] years for the items shown below. **Tissue regeneration** • Observation by gross examination of appearance at the implanted site • Evaluation by histological examination of tissue regeneration status at the implanted site **Calcification** • Evaluation by [redacted] of calcification status at the implanted site • Calculation of calcium amount using calibration curves
Study of long-term implantation in animal vessel wall ([redacted] years) Test device: Synfolium (N = [redacted] for [redacted] years)	An oval shaped patch (1 cm × 2 cm) of the test device was implanted at the defect site of the descending thoracic aorta of beagles. The device was evaluated for the items shown below at [redacted] years. **Tissue regeneration** • Observation by gross examination of appearance at the implanted site • Evaluation by histological examination of tissue regeneration status at the implanted site **Mechanical evaluation** Tensile strength and stretching studies, PLLA molecular weight **Calcification** • Evaluation by [redacted] of calcification status at the implanted site

In the study of implantation in an animal vessel wall, Synfolium was implanted in the descending thoracic aorta of beagles to investigate the early effects ([redacted] and [redacted] weeks after implantation) of the device on the appearance at the implanted site, thrombogenicity/rupture/aneurysmal change/blood flow/tissue healing of the luminal surface, and local reaction. There were no systemic effects of Synfolium, or effects on blood flow/rupture/stenosis/aneurysmal change of the luminal surface of the vessel wall at the implanted site. Special staining indicated that the blood vessel lumen of Synfolium had presented [redacted] which is considered to be [redacted], an indicator of tissue regeneration, at [redacted] weeks after implantation, suggesting healing/stabilization. There were no clear efficacy or safety problems at [redacted] weeks after implantation. Additionally, there were no differences between the front or back side of Synfolium facing the luminal surface. No clear differences were noted compared with Gore-Tex EPTFE Patch II.

In the study of long-term implantation in an animal vessel wall ([redacted] years, [redacted] years), biodegradable PLLA was implanted in the descending thoracic aorta of beagles to evaluate the efficacy and safety of the test material after it is degraded and absorbed. The study was conducted to investigate the long-term effects ([redacted] years, [redacted] years) on the appearance at the implanted site, tissue regeneration status, mechanical evaluation, and PLLA molecular weight. The test material used was a prototype PLLA whose purity is slightly lower than that of Synfolium, but there was no significant difference in the degradation behavior. The use of the test material for the evaluation of tissue regeneration and mechanical strength was determined to be appropriate. The results of the gross examination and histological examination at [redacted] and [redacted] years after implantation showed typical vessel wall repair. There were no safety problems attributable to Synfolium such as morphological anomalies (e.g., rupture, aneurysmal change, and stenosis), inflammatory response, and calcification in the long term after initial repair. The area where living tissue was present between the lumen and adventitia at the implanted site of the test material expanded in width at [redacted] years after implantation compared with that at [redacted] years after implantation with the animal tissue mainly composed of growing collagen fibers and vasa vasorum filling the gap as phagocytosis and elimination of PLLA progressed. The mechanical evaluation (tensile strength and stretching tests) revealed the following: degradation of PLLA yarn had progressed both at [redacted] and [redacted] years after implantation; however, the tensile strength test results suggested that the stress at the implanted area of Synfolium was greater than that estimated for a vessel wall under physiological conditions.

The comparison study of long-term implantation in an animal vessel wall was conducted to evaluate whether Synfolium can prevent problems such as material deterioration, calcification, and stenosis in the long term after initial repair, which are the development concepts. In the study, Synfolium or the approved product, Gore-Tex EPTFE Patch II or Bovine Pericardial Patch, was implanted in the descending thoracic aorta of beagles. The results of gross evaluation and

histological evaluation [redacted] years after implantation showed formation of intima containing endothelial cells in the lumen, with no macroscopic morphological anomalies. The condition of regenerative tissue varied among patch materials. In contrast to the approved products in which biological reactions continued to be detected, tissue was regenerated in an ongoing manner in all vessel wall layers of the area Synfolium was implanted, and no phagocytosis or inflammatory cell infiltration were present near regenerative tissue at the implanted site. To evaluate calcification, [redacted], [redacted], and the amount of calcium calculated from the calibration curves for calcium was used as the indicator for calcification. Calcification was observed around the suture site area of the implanted sites of Synfolium and "Gore-Tex EPTFE Patch II," one of the approved products. A significant amount of calcium was detected in the patch material in [redacted] animals in which "Bovine Pericardial Patch" was implanted.

In the study of long-term implantation in an animal vessel wall ([redacted] years), Synfolium was implanted in the descending thoracic aorta of beagles to evaluate even longer efficacy and safety including tissue regeneration, mechanical evaluation, and calcification. The entire Synfolium patch was encapsulated with tissue primarily composed of collagen fiber. The entire luminal surface of the implanted area was covered with a layer of epithelial cells. Hyperplasia of [redacted] at the implanted area was partially noted, while hyperplasia of [redacted] was not observed. Formation of animal tissue with inner and outer vessel wall communication was observed over a wide area. Inflammatory response had subsided and no calcification or calcium deposition, the cause of calcification, was observed in regenerative tissue formed by Synfolium.

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

PMDA asked the applicant to explain the following issues.

(a) The stretching function, which is a long-term advantage of Synfolium, is difficult to evaluate in a short-term clinical study. Explain how data from animal studies can be interpreted in this regard.

(b) Taking into account of gelatin degradation, PLLA degradation, tissue regeneration, and growth of the heart and blood vessels, explain whether it is possible that 1) stenosis, etc. may occur if the growth exceeds the speed of Synfolium degradation; 2) blood leak, etc. may occur if the speed of Synfolium degradation and organs growth exceed the speed of tissue regeneration.

The applicant's response:

(a) The diameter of the main pulmonary artery greatly increases from birth to school age, during the period when the stretching function of Synfolium is expected to be most advantageous.

In the opinions of clinicians, the initial repair with a device like Synfolium is generally performed at around 1 year of age, and reoperation is performed at around 5 years of age. One of the reasons for performing reoperations is that the conventional patches are non-stretchable. Synfolium is intended to be used primarily in the pulmonary artery system. The diameters of the main pulmonary artery of children aged 1 year (body surface area [BSA] 0.4 m^2) and 5 years (BSA 0.7 m^2)[9] are estimated to be approximately 1.14 cm and 1.61 cm, respectively, which is roughly a 1.41-fold increase. The results of the *in vitro* degradation study showed that the [redacted] strength of Synfolium was [redacted] after [redacted] years of [redacted] in [redacted], and the results of the long-term implantation study in animal vessel walls at [redacted] years after implantation showed that the structure composed of PET yarn stretched as a result of fraying after an external force was applied to the structure. Given the operation timeframe in the clinical practice as well as the non-clinical study results of Synfolium, PLLA is inferred to fray in the body to activate the stretching function of Synfolium after the initial repair at around 1 year of age and before the reoperation. The diameter of the main pulmonary artery in individuals aged 18 years (BSA 1.6 m^2) is approximately 2.22 cm, roughly a 1.95-fold increase from that of a 1-year-old. The stretching study has shown that Synfolium stretches to ≥2-fold its original length after PLLA degradation, and the stretching function is expected to continue for up to 18 years after the initial repair at around 1 year.

(b) The results of non-clinical studies (degradation of gelatin, PLLA, and tissue regeneration) are shown below and are organized in the schematic diagram in Figure 2.

The study of implantation in an animal vessel wall showed that Synfolium was covered entirely with tissue (primarily endothelial cells and collagen fiber) by [redacted] weeks after implantation, gelatin is gradually degraded by [redacted] and significantly decreased at [redacted] weeks. The results of an in vitro degradation study and the study of long-term implantation in an animal vessel wall showed that PLLA was degraded over ≥[redacted] years by nonspecific hydrolysis.

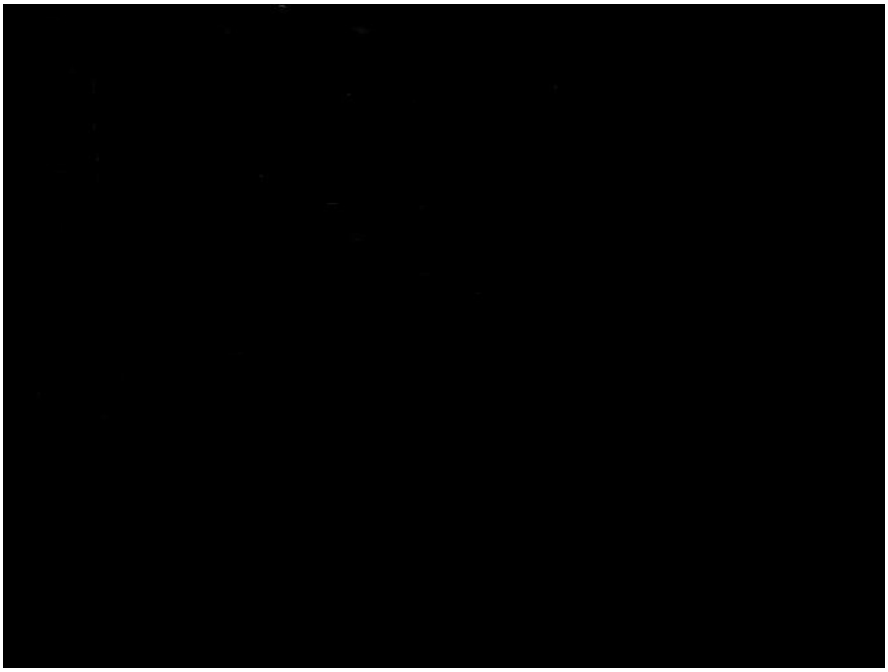

Figure 2. Summary of non-clinical study results (schematic diagram)

As discussed above, when implantation of Synfolium is assumed to be performed, the patient is estimated to grow roughly 1.41-fold during the period from 1 year of age, when the initial repair is typically performed, to 5 years of age when reoperation is often performed.

1) No possibility of stenosis, etc. caused by slow degradation of Synfolium
   Approximately ≥[redacted] years after implantation of Synfolium, PLLA degradation progresses, and the implanted area can be expanded to [redacted] times the initial area ([redacted] times MD × [redacted] times TD). This period is shorter than "4 to 5 years after surgery," the period in which the stretching function is anticipated; therefore, it is unlikely that the patient growth exceeds the degradation of PLLA.
2) No possibility of blood leak, etc. caused by slow tissue regeneration and fast degradation of Synfolium and organ growth
   At [redacted] weeks after implantation, Synfolium will be covered with regenerated tissue. Gelatin will be degraded by [redacted]. Degradation of gelatin occurs after the patch is covered with tissue, and tissue will replace the area of degraded gelatin; therefore, blood leak is unlikely to occur. In the studies of Synfolium implantation in an animal vessel wall, there was no evidence of blood leak in any of the animals.

PMDA's view on the performance of Synfolium:
Because the stretching function is affected by tissue regeneration, PMDA considers that it is not appropriate to conclude that performance has been sufficiently evaluated based on the currently available animal study results; however, given the results of the stretching study and other data,

Synfolium is expected to have advantages in its stretching function. As for the reduction in calcification, PMDA understands the applicant's explanation that the animal study results showed a trend toward reduction in calcification, given the small sample size and species difference, long-term data in humans should be closely evaluated. Furthermore, given that the degradation behavior of PLLA and tissue regeneration at the site of Synfolium implantation have been confirmed and that no safety concerns arising from the characteristics of Synfolium have been identified, although long-term observation is needed, Synfolium is expected to provide unique advantages.

On the basis of the above performance data, PMDA concluded that there were no particular problems.

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

3.A Summary of the data submitted

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

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of Synfolium to the Essential Principles.

(1) The conformity of Synfolium to Article 1, which stipulates preconditions, etc. for designing medical devices (particularly requirements for users, such as the expected level of technical knowledge and experience, and the expected level of education and training for users).

PMDA's view:

As described later in Section "6.B Outline of the review conducted by PMDA," to ensure its risk-benefit balance of Synfolium, given that none of the patients enrolled in the clinical study underwent implantation in the aorta, when Synfolium is used in the aorta, it is important to appropriately select qualified users and institutions that can implant Synfolium in the aorta and comply with the proper use guidelines. For this reason, PMDA decided to add approval conditions to ensure that necessary measures are taken.

(2) The conformity of Synfolium to Article 2, which stipulates risk management throughout the life cycle of medical devices.

PMDA's view:

As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," because only a small number of patients were evaluated in the clinical study of Synfolium, efficacy and safety in clinical use should be evaluated, and additional risk minimization measures should be taken as necessary; therefore, PMDA instructed the applicant to conduct a use-results survey. Because none of the patients enrolled in the clinical study underwent implantation in the aorta, it was decided to add another approval condition to ensure that the survey covers all of the patients who will be undergoing implantation in the aorta.

(3) The conformity of Synfolium to Article 3, which stipulates the performance and function of medical devices, and to Article 6, which stipulates the efficacy of medical devices.

PMDA's view:

As described later in Section "6.B Outline of the review conducted by PMDA," based on the results from the clinical study, Synfolium can be used in an effective and safe manner equivalent to the approved products provided that the user has a good understanding of the product characteristics and information including detailed procedural precautions are provided. Therefore, there was no problem with the conformity of Synfolium to Articles 3 and 6.

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

PMDA's view:

As described later in Section "6.B Outline of the review conducted by PMDA," in order to maintain the risk-benefit balance of Synfolium, it is important to understand the characteristics before using Synfolium. Therefore, relevant information should be disseminated through the package insert, the proper use guidelines, and by other means.

On the basis of the above, PMDA comprehensively reviewed the conformity of Synfolium to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its implementation status in accordance with JIS T 14971 "Medical devices—Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the discussion presented in Section "3.B Outline of the review conducted by PMDA" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on inspections implemented during the manufacturing process of Synfolium and the sterilization method (implementation status of sterilization validation, ethylene oxide sterilization residuals, bacterial endotoxin testing).

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process and concluded that there were no particular problems.

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

6.A Summary of the data submitted

The applicant submitted data from Study OFT-G1-301, a multicenter, prospective, single-arm clinical study of Synfolium.

Study OFT-G1-301 was conducted at 6 study centers in Japan to evaluate the efficacy and safety of Synfolium in patients with congenital heart disease undergoing cardiac repair. In this study, Synfolium was used in 34 subjects. Table 2 shows the summary of the study.

Table 2. Summary of Study OFT-G1-301

Item	Outline
Objective	To evaluate the safety and efficacy of the cardiovascular repair patch OFT-G1 in patients with congenital heart disease undergoing cardiac repair
Study design	Multicenter, prospective, single-arm
Study population	Patients with congenital heart disease
Inclusion criteria	Eligible patients are those who meet all the following criteria: (1) Patients who require thoracotomy (2) Patients who are to undergo one of the following operative procedures: 1) Atrial septal defect closure 2) Ventricular septal defect closure* 3) Right ventricular outflow tract reconstruction 4) Pulmonary angioplasty 5) Aortoplasty * In Cohort 1, only those patients who were to undergo ventricular septal defect closure alone were included (3) Patients who have ≥1 site in any of the heart septum, the outer wall, and vessel wall to be repaired with prosthetic material (4) Patients or their legally acceptable representative who can provide written informed consent

Exclusion criteria	Patients are excluded if they meet any of the following criteria: (1) Preoperative exclusion criteria 1) Patients requiring emergency surgery 2) Patients requiring heart surgery with an Aristotle score[10] (a complexity score for heart surgery procedures) of Level 4 3) Patients with non-cardiac disease significantly increasing surgical risk, severe non-cardiac disease with life expectancy of <6 months, or progressive non-cardiac disease (e.g., liver failure, renal failure, cancer) 4) Patients weighing <3 kg 5) Patients with coagulation test abnormality (deviation from institutional normal range) and who are determined to be ineligible to participate in the study at the discretion of the investigator or subinvestigator (hereinafter referred to as the "investigator") 6) Patients with blood disorders such as thrombocytopenia, anemia, leukemia, and who are determined to be ineligible to participate in the study at the discretion of the investigator 7) Patients diagnosed with familial arrhythmia (e.g., Brugada syndrome, long QT syndrome [LQT]) 8) Patients diagnosed with arrhythmias based on preoperative ECG and who are determined to be ineligible to participate in the study at the discretion of the investigator 9) Patients with active systemic infection 10) Patients with a history of past surgery within 3 months prior to obtaining consent Provided, however, that this does not apply to the following cases: − If the patient received upfront surgery for congenital heart disease − If the surgery is less invasive to the whole body, and postoperative course is uneventful in the opinion of the investigator 11) Patients who are scheduled to undergo another surgery within 3 months after submitting informed consent in addition to the cardiac surgery in the study. Provided, however, that this does not apply to the following case: − If the surgery is less invasive to the whole body, and the investigator determined that there is no problem with participating in the study. 12) Patients who participated in another clinical trial within 3 months prior to providing informed consent, or who are currently participating in, or scheduled to participate in another clinical trial within the next 1 year. 13) Patients who have a history of allergic reactions or hypersensitivity to the following drugs − Contrast media − Anticoagulants, antiplatelet drugs − Products of porcine origin 14) Patients who are pregnant or lactating at the time of providing informed consent, and patients who are unable to comply with contraception for up to 1 year after surgery 15) Other cases where the investigator determined that the patient is not suitable to be the subject of this study (2) Intraoperative exclusion criteria 1) Patients who have local infection at the planned implant site 2) Other cases where the investigator determined during surgery that the patient is not suitable to be the subject of this study.
Number of patients	30 patients at the time of planning (enroll study patients so that ≥60% of subjects are those "who underwent pulmonary angioplasty and/or right ventricular outflow tract reconstruction") Consent obtained: 36 subjects In the analyses: efficacy (full analysis set [FAS]): 34 subjects efficacy (per protocol set [PPS]): 34 subjects safety: 34 subjects

Primary endpoint	The surgical success rate in the year following surgery Definition of surgical success: The surgery is defined as successful if none of the following apply to the subject. • Death caused by malfunctions associated with Synfolium • Reoperation or reintervention* at the implanted site is required because of malfunctions associated with Synfolium * Reintervention is determined based on the following: • Reoperation due to malfunctions associated with Synfolium: when Synfolium is used for patch augmentation of the right ventricular outflow tract and at the same time a valve leaflet is constructed using Gore-Tex, any reoperation due to pulmonary valve regurgitation, etc. caused by the Gore-Tex valve leaflet will not be included. However, if the shape and structure of the base of the blood vessel and valve becomes distorted due to a decline in the strength of Synfolium, leading to valve dysfunction, this case is determined as unsuccessful. • Reintervention at the implanted site due to malfunctions associated with Synfolium: pharmacotherapy is not included.
Secondary endpoint	(1) Presence or absence of residual lesions detected by echocardiography 1) Presence or absence of residual lesions Definition of presence or absence of residual lesions: Residual lesions is defined as absent when the following applies to the implanted site of the test device. • If "no" applies to all items for residual lesions • If "yes" applies to either one or both of the following items on residual lesions, Structural leak* and Residual leak,** while "no" applies to the additional hemostasis and is considered to be a clinically insignificant finding, and furthermore, "no" applies to all remaining items. * A lesion attributable to the physical properties of Synfolium. Residual shunt and blood leak caused by cracking and rupture after implantation ** A lesion attributable to surgical technique regardless of the type of materials implanted. Residual shunt and blood leak caused by gap between the patch and tissue 2) Blood leak at the implanted site 3) Freedom from restenosis 4) Cardiac function evaluation by M-mode echocardiography (2) Presence or absence of reoperation or reintervention at the implanted site caused by malfunctions associated with Synfolium (3) Duration of surgery, intraoperative blood loss, intraoperative blood transfusion (4) Presence or absence of reintervention (5) Operability, usefulness (6) Adverse events, etc.
Follow-up period	3 years
Study center	6 centers
Study period	May 2019 to February 2024

Taking into account of the objectives of Study OFT-G1-301, i.e., to evaluate the efficacy and safety of Synfolium by verifying the equivalence with the similar devices, "the surgical success rate in the year following surgery" was selected as the primary endpoint. On the basis of the results of similar devices, the success criterion was the lower bound of the 90% CI exceeding the threshold of [redacted]%. Because not all surgical procedures can be covered, it was designed to include surgery in a low-pressure system, e.g., the atrial septal defect closure and tetralogy of Fallot (pulmonary artery area) and a high-pressure system, e.g., the ventricular septal defect closure. Since there is no novelty in the surgical procedure, no roll-in cases were established. However, given that Study OFT-G1-301 was the first in human (FIH) study, the study proceeded while closely monitoring the safety. In Cohort 1, patients were to undergo ventricular septal defect

closure with Synfolium as a sole procedure. After examining the safety evaluation results in the first patient at [redacted] months, the investigator continued the study after determining the use of Synfolium in the second and subsequent patients. The Data Monitoring Committee (DMC) confirmed that there were no safety concerns [redacted] in [redacted] of Cohort 1, and Cohort 2 was started.

Figure 3 shows the analysis sets of Study OFT-G1-301. Of the 36 subjects who provided signed informed consent, 2 subjects were excluded because Synfolium was not used due to changes in surgical procedure during surgery. The remaining 34 subjects underwent cardiac repair using Synfolium. A total of 10 subjects had protocol deviations related to informed consent (1 subject), examination/observation (2 subjects), and clinical trial procedure (8 subjects). Since these were not serious protocol deviations, the subjects were not excluded from the FAS, PPS, and safety analysis set.

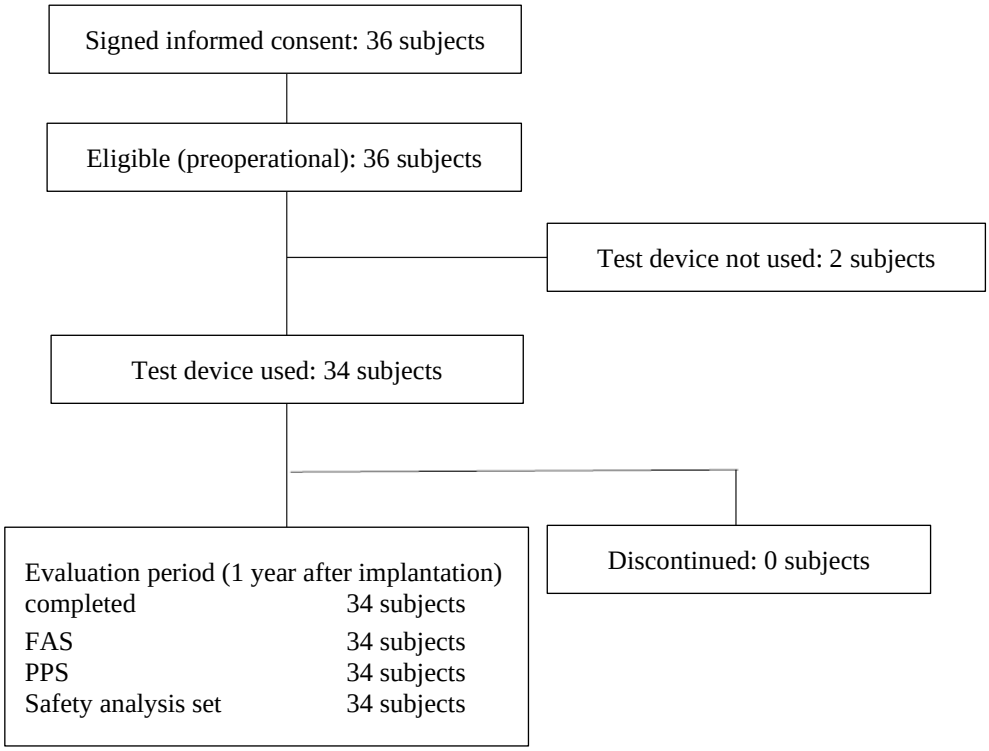

Figure3. Disposition of subjects in analysis sets

6.A.(1) Patient characteristics

Table 3 shows the demographic characteristics and baseline characteristics of subjects in the analysis set. The subjects (N = 34) had a median age (range) of 1.5 (0-59) years. Of 8 subjects aged <1 year, 3 subjects were 4, 8, and 9 months of age (1 subject each), 2 subjects were 10 months of age, and 3 subjects were 11 months of age.

The following were types of surgical procedures performed: atrial septal defect repair in 17.6% (6 of 34) of subjects, ventricular septal defect repair in 11.8% (4 of 34) of subjects, pulmonary angioplasty in 58.8% (20 of 34) of subjects, and right ventricular outflow tract reconstruction in 26.5% (9 of 34) of subjects. No subjects underwent aortoplasty. The percentage of subjects who underwent pulmonary angioplasty and/or right ventricular outflow tract reconstruction was 70.6% (24 of 34) of subjects, which satisfied the target of "≥60% of subjects in the entire study are those who underwent pulmonary angioplasty and/or right ventricular outflow tract reconstruction using Synfolium" as prespecified in the protocol to ensure that atrial septal defect closure and ventricular septal defect closure were not over-represented among the surgical procedures. Subjects who underwent >1 type of surgical procedure (combination of right ventricular outflow tract reconstruction and pulmonary angioplasty) accounted for 14.7% (5 of 34) of subjects. The complexity of surgery, as measured by the Aristotle Score, was as follows: [redacted] of 34 subjects ([redacted]%) underwent Level 1, [redacted] of 34 subjects ([redacted]%) underwent Level 2, and [redacted] of 34 subjects ([redacted]%) underwent Level 3. Of the 12 subjects who underwent pulmonary valve reconstruction, 10 subjects (83.3%) received a pulmonary valve replacement or underwent pulmonary valvuloplasty. In Study OFT-G1-301, planned implanted sites were roughly grouped into sites in the low-pressure system and those in the high-pressure system, and surgical procedures to be used for the sites were included in the inclusion criteria. Thirty subjects underwent surgery at sites in a low-pressure system, e.g., atrial septal defect closure and tetralogy of Fallot (pulmonary artery area) while 4 subjects underwent surgery at sites in a high-pressure system, e.g., ventricular septal defect closure. Therefore, Synfolium was used at both low-pressure and high-pressure sites as initially planned.

Table 3. Demographic characteristics and baseline characteristics (N = 34)

Demographic and baseline characteristics	
Age (years)	
Mean ± standard deviation (SD) (median)	9.1 ± 14.6 (1.5)
Minimum, Maximum	0, 59
Age (years), N (%)	
<1	8 (23.5)
≥1 and <2	9 (26.5)
≥2 and <6	6 (17.6)
≥6 and <18	4 (11.8)
≥18	7 (20.6)
Height (cm)	
Mean ± SD (median)	102.39 ± 38.96 (80.30)
Minimum, Maximum	5[redacted], 17[redacted]
Body weight (kg)	
Mean ± SD (median)	21.33 ± 19.56 (11.10)
Minimum, Maximum	5.[redacted], 61.[redacted]
Body weight (kg), N (%)	
<3	0 (0.0)
≥3 and <10	16 (47.1)
≥10 and <20	8 (23.5)
≥20 and <50	4 (11.8)
≥50	6 (17.6)
Sex, N (%)	
Male	20 (58.8)
Female	14 (41.2)
Primary disease, N (%)	
Atrial septal defect	4 (11.8)
Ventricular septal defect	3 (8.8)
Pulmonary artery atresia	2 (5.9)
Pulmonary valve stenosis	0 (0.0)
Tetralogy of Fallot	10 (29.4)
Patent ductus arteriosus	0 (0.0)
Others	15 (44.1)
Aristotle Score Level, N (%)	
Level 1	2 (5.9)
Level 2	18 (52.9)
Level 3	14 (41.2)
Number of operations, N (%)	
First operation	16 (47.1)
Reoperation	18 (52.9)
Implantation site, N (%)	
Ventricular septum	4 (11.8)
Atrial septum	6 (17.6)
Aorta	0 (0.0)
Pulmonary artery	17 (50.0)
Right ventricular outflow tract reconstruction	12 (35.3)
Heart septal defect closure (atrial septum + ventricular septum)	10 (29.4)
Augmentation in the outer vessel wall of the heart (pulmonary artery + right ventricular outflow tract)	24 (70.6)
Surgical procedure, N (%)	
Atrial septal defect closure	6 (17.6)
Ventricular septal defect closure	4 (11.8)
Pulmonary angioplasty	20 (58.8)
Aortoplasty	0 (0.0)
Right ventricular outflow tract reconstruction	9 (26.5)
Pulmonary angioplasty, right ventricular outflow tract reconstruction	24 (70.6)
Pulmonary valve reconstruction, N (%)	
Yes	12 (35.3)

Demographic and baseline characteristics	
No	22 (64.7)
Surgical procedure for pulmonary valve reconstruction, N (%)	
Pulmonary valve replacement or pulmonary valvuloplasty	10 (29.4)
Right ventricular outflow tract reconstruction	1 (2.9)
Commissurotomy	1 (2.9)
Materials used for pulmonary valve reconstruction, N (%)	
None	1 (2.9)
Mosaic 25 mm[a)]	5 (14.7)
INSPIRIS 25 mm[b)]	2 (5.9)
Yamagishi conduit 20 mm	2 (5.9)
Yamagishi conduit 18 mm	1 (2.9)
0.1 mm ePTFE Patch	1 (2.9)
Intraoperative blood transfusion, N (%)	
Yes	27 (79.4)
No	7 (20.6)
Residual lesions, N (%)	
Present	11 (32.4)
Absent	7 (20.6)
Residual lesions (category), N (%)	
Surface thickening	0 (0.0)
Blood clot formation	0 (0.0)
Calcification	0 (0.0)
Restenosis	6 (17.6)
Baffle leak closure	1 (2.9)
Residual ventricular septal defect	1 (2.9)
Pulmonary valve regurgitation	3 (8.8)
Enlargement deformation or aneurysm, and pulmonary valve regurgitation	1 (2.9)
Duration of drainage[c)] (days)	
Mean ± SD (median)	3.5 ± 1.7 (3.0)
Minimum, Maximum	2, 11
Duration of hospitalization[d)] (days)	
Mean ± SD (median)	19.1 ± 10.6 (16.5)
Minimum, Maximum	8, 52

a) "Mosaic Bioprosthetic Valve" (Approval No. 21100BZY00508000)

b) "INSPIRIS RESILIA Aortic Valve" (Approval No. 22900BZX00053000)

c) Duration of drainage = drainage completion date − drainage starting date

d) Duration of hospitalization = discharge date − operation date

6.A.(2) Status of use of Synfolium

The mean ± SD of the area (π × major axis [mm] /2 × minor axis [mm] /2) of Synfolium used in 34 subjects was 821.27 ± 920.03 mm^2. The mean ± SD area of the patch used by implantation site was 90.28 ± 15.03 mm^2 for the ventricular septum, 536.68 ± 512.23 mm^2 for the atrial septum, 407.05 ± 379.11 mm^2 for the pulmonary artery, and 1451.86 ± 1221.06 mm^2 for the right ventricular outflow tract (Table 4).

Table 4. Area of Synfolium used (by implantation site)

Implantation site	N	Area used[a)] Mean ± SD (median) Minimum, Maximum
Total	34	821.27 ± 920.03 (562.85) 78.5, 3925.0
(By implantation site)		
Ventricular septum	4	90.28 ± 15.03 (86.35) 78.5, 109.9
Atrial septum	6	536.68 ± 512.23 (411.73) 91.8, 1413.0
Aorta	0	—
Pulmonary artery	17[b)]	407.05 ± 379.11 (254.34) 153.1, 1648.5
Right ventricular outflow tract	12[b)]	1451.86 ± 1221.06 (1314.88) 212.0, 3925.0

[a)] Area of the test device used = π × (major axis [mm] /2) × (minor axis [mm] /2)
[b)] Including subjects who received implants in both sites

6.A.(3) Status of procedures performed

Synfolium was implanted in a total of 41 sites: 4 sites in the ventricular septum in 4 of 34 subjects (11.8%), 7 sites in the atrial septum in 6 of 34 subjects (17.6%), 18 sites in the pulmonary artery in 17 of 34 subjects (50.0%), and 12 sites in the right ventricular outflow tract in 12 of 34 subjects (35.3%). Synfolium was not used in the aorta.

6.A.(4) Concomitant use with other patches

In Study OFT-G1-301, concomitant use of patches other than Synfolium was allowed for limited purposes. Gore-Tex EPTFE Patch II, in which the concomitant use was allowed, was used in 47.1% (16 of 34) of subjects. The most common purpose of its use was the repair of ventricular or atrial septal defects in 29.4% (10 of 34) of subjects, followed by pericardium repair in 14.7% (5 of 34) of subjects, and prevention of adhesion in 8.8% (3 of 34) of subjects.

6.A.(5) Study results

6.A.(5).1) Primary endpoint

The point estimate for the primary endpoint “the surgical success rate in the year following surgery” was 100% (34 of 34) of subjects, with a 90% confidence interval of 91.6% to 100.0%. The lower limit 91.6% exceeded the prescribed threshold of [redacted]% and the target performance of Synfolium was achieved. Because the 95% confidence interval was 89.7% to 100.0%, the lower limit exceeded the prescribed threshold of [redacted]%.

6.A.(5).2) Secondary endpoints

6.A.(5).2).(a) Presence/absence of residual lesions by echocardiography

i) Presence/absence of residual lesions

All implanted sites were examined by the investigator using echocardiographic images at each examination time point for evidence of 7 categories (surface thickening, blood clot formation, structural leak, residual leak, calcification, restenosis, enlargement deformation or aneurysm) to evaluate the presence/absence of residual lesions. “Restenosis” occurred in 1 subject who underwent Synfolium implantation in the right ventricular outflow tract at 6 months and 1 year after surgery, and residual lesions was determined to be “present.”

ii) Blood leak at the implanted site

Residual leak occurred in 3 subjects, with the severity rated as “trivial” in all subjects based on a 4-point grading scale (1 = severe, 2 = moderate, 3 = mild, and 4 = trivial). No additional treatment was performed for these cases of blood leak. None of the findings was considered to be clinically meaningful because there was “no change in circulatory dynamics” (2 subjects) and “no cardiac failure symptoms” (1 subject).

iii) Freedom from restenosis

The freedom from restenosis (sites with no restenosis / total sites of implantation into the vessel × 100) at the echocardiography time points (hospital discharge, 3 months, 6 months, and 1 year after surgery) was calculated. The freedom from restenosis at the examination time points was 100.0% (30 of 30 sites), 100.0% (30 of 30 sites), 96.7% (29 of 30 sites), and 96.7% (29 of 30 sites).

Stenosis reported at 6 months and 1 year after surgery occurred in the main pulmonary artery distal to the implanted site of the subject in whom a single-valved right ventricular outflow tract patch, prepared in advance by attaching a valve made from Gore-Tex EPTFE Patch II (0.1 mm) to Synfolium, was implanted in the pulmonary artery (including right ventricular outflow tract). The stenosis was determined to be mild in severity, and no additional treatment was performed. Because stenosis could have occurred even without Synfolium, it was reported as stenosis having an unknown causal relationship to Synfolium.

iv) Cardiac function evaluation by M-mode echocardiography

M-mode echocardiography was performed to calculate the fractional shortening (FS) and evaluate cardiac function. There were no notable changes.

6.A.(5).2).(b) Presence or absence of reoperation or reintervention at the implanted site caused by malfunctions associated with Synfolium

Reoperation and reintervention were performed in the vicinity of the implanted site of Synfolium in 1 of 34 subjects. The major cause was that the subject's own pulmonary artery became taut because the prosthetic vessel used for this subject was too short. Therefore, it was concluded that no subjects underwent reoperation or reintervention caused by malfunctions associated with Synfolium.

6.A.(5).2).(c) Duration of surgery, intraoperative blood loss, intraoperative blood transfusion

Duration of surgery in 34 subjects who were implanted with Synfolium was 358.7 ± 184.6 minutes (the mean ± SD). Similarly, the intraoperative blood loss was 312.5 ± 440.6 mL, and intraoperative blood transfusion was 372.3 ± 396.7 mL (red blood cell), 402.4 ± 490.0 mL (plasma), 201.1 ± 187.2 mL (platelet), and 480.0 mL (whole blood). There were no notable findings related to the implantation sites and procedure employed in Study OFT-G1-301.

During surgery, 27 subjects received blood transfusion. The sites of Synfolium implantation in patients who did not receive blood transfusion were intracardiac septum (4 subjects) and outer vessel wall of the heart (3 subjects). The latter 3 subjects were adult patients who underwent pulmonary valve replacement.

The subgroup analysis by implanted site showed that the operation duration was the longest for the right ventricular outflow tract, followed by pulmonary artery, atrial septum, and ventricular septum. The subgroup analysis by intraoperative blood loss showed similar trends. In subjects where Synfolium was implanted into the outer vessel wall of the heart (pulmonary artery and right ventricular outflow tract), operation duration was longer and intraoperative blood loss was greater than in those where Synfolium was implanted into the intracardiac septum (atrial septum and ventricular septum).

The subgroup analysis by the number of surgeries (1 operation vs ≥2 operations for the primary disease) showed that subjects who underwent ≥2 surgeries had longer operation time and more interoperative blood loss than those who underwent 1 operation.

6.A.(5).2).(d) Presence or absence of re-thoracotomy for hemostasis

Re-thoracotomy for hemostasis was performed in 1 of the 34 subjects to repair pneumothorax caused by adhesiolysis that had occurred during surgery for the primary disease, to restore hemostasis, and remove hematoma. It was concluded that the re-thoracotomy for hemostasis was

not caused by malfunctions of Synfolium.

6.A.(5).2).(e) Operability, usefulness

The 5 items of operability (ease of cutting, ease of needle/thread penetration, resistance to fraying, compatibility with tissue, and degree of blood leak after implantation) and 2 items of utility (level of satisfaction and recommendation) were evaluated.

i) Operability

The rating scores of 5, 4, and 3 (5 = excellent, 4 = good, and 3 = fair) were summed for each operability item as follows: ease of cutting, 94.1% (32 of 34) of subjects; ease of needle/thread penetration, 97.1% (33 of 34) of subjects; resistance to fraying, 91.2% (31 of 34) of subjects; compatibility with tissue, 82.4% (28 of 34) of subjects; and degree of blood leak after implantation, 67.6% (23 of 34) of subjects.

ii) Utility

The rating scores of 5 and 4 (5 = excellent, 4 = good) for satisfaction of utility were summed to 58.8% (20 of 34) of subjects while the rating scores (5 = strongly recommend, 4 = recommend) were summed to 64.7% (22 of 34) of subjects.

6.A.(5).3) Adverse events, etc.

6.A.(5).3).(a) Adverse events

Table 5 shows the adverse events reported in Study OFT-G1-301. The adverse events for which a causal relationship to Synfolium could not be ruled out ("related," "probably related," "possibly related," or "unknown") as determined by the investigator were handled as "device-related adverse events." The validity of the investigator assessment of causal relationship to Synfolium were confirmed by the DMC, an independent organization of experts that reflects objective opinions.

The incidence of adverse events was 88.2% (30 of 34) of subjects. The incidence of "adverse events occurred from the date of surgery up to 3 months" was 76.5% (26 of 34) of subjects, and "those from 3 months up to 1 year after surgery" was 55.9% (19 of 34) of subjects. The incidence of device-related adverse events was 11.8% (4 of 34) of subjects, and the details were "pulmonary artery stenosis," "mediastinal haematoma," "pyrexia," and "post procedural haemorrhage" 2.9% (1 of 34) of subjects each, and all events occurred within 3 months of surgery.

The incidence of serious adverse events was 14.7% (5 of 34) of subjects. Serious adverse events occurred "from the date of surgery up to 3 months" in 11.8% (4 of 34) of subjects and "from 3

months up to 1 year after surgery" in 2.9% (1 of 34) of subjects. The details of serious adverse events were "upper respiratory tract infection," "atrial tachycardia," "pulmonary artery stenosis," "pulmonary vein stenosis," and "post procedural haematoma" (1 subject each, 2.9%). No adverse events led to death or study discontinuation. A causal relationship to the study device was denied for all serious adverse events. "Aneurysmal change," which was classified as an adverse event of special interest, did not occur during the evaluation period.

Table 5. Adverse events (N = 34)

	Up to 3 months after surgery n (%) [m]	From 3 months up to 1 year after surgery n (%) [m]	Overall n (%) [m]
All adverse events	26 (76.5) [53]	19 (55.9) [39]	30 (88.2) [92]
All device-related adverse events	4 (11.8) [4]	0 (0.0) [0]	4 (11.8) [4]
Pulmonary artery stenosis	1 (2.9) [1]	0 (0.0) [0]	1 (2.9) [1]
Mediastinal haematoma	1 (2.9) [1]	0 (0.0) [0]	1 (2.9) [1]
Pyrexia	1 (2.9) [1]	0 (0.0) [0]	1 (2.9) [1]
Post procedural haemorrhage	1 (2.9) [1]	0 (0.0) [0]	1 (2.9) [1]
Serious adverse events	4 (11.8) [4]	1 (2.9) [1]	5 (14.7) [5]
Upper respiratory tract infection	1 (2.9) [1]	0 (0.0) [0]	1 (2.9) [1]
Atrial tachycardia	0 (0.0) [0]	1 (2.9) [1]	1 (2.9) [1]
Pulmonary artery stenosis	1 (2.9) [1]	0 (0.0) [0]	1 (2.9) [1]
Pulmonary vein stenosis	1 (2.9) [1]	0 (0.0) [0]	1 (2.9) [1]
Post procedural haematoma	1 (2.9) [1]	0 (0.0) [0]	1 (2.9) [1]
Device-related adverse events	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

n, number of subjects developing the events; (incidence, n / N); [m, number of adverse events occurring]

One of the subjects who developed serious pulmonary artery stenosis had primary disease of tricuspid atresia. A Fontan procedure, in which Synfolium was used in the left pulmonary artery simultaneously with anastomosis of an 18-mm diameter PTFE artificial vessel with the right pulmonary artery was performed, and a procedure for pulmonary artery closure was also performed. Six days after surgery, left pulmonary artery stenosis was found by echocardiography between the PTFE artificial vessel and the implanted Synfolium (diagnosis confirmed 18 days after surgery). On 22 days after surgery, percutaneous transluminal balloon angioplasty using a cardiac catheter was performed to treat the left pulmonary artery stenosis. Although the pressure gradient decreased, stenosis remained due to inadequate dilation, and pulmonary artery plasty was performed 30 days after surgery to expand the narrowed area with a PTFE patch. The findings at reoperation indicated that the pulmonary artery stenosis described above was primarily caused by the slightly short 18-mm PTFE artificial vessel used in the Fontan procedure, leading the patient's own pulmonary artery to become taut. Therefore, the investigator determined that the stenosis was caused by a procedural problem unrelated to Synfolium. After the review, the DMC concluded that there was no causal relationship to Synfolium according to the category of acceptance criteria in Table 6 because the data did not clearly indicate a possibility of reasonable

causal relationship between Synfolium and reoperation/reintervention.

Table 6. Acceptance criteria for causal relationship by DMC

Category	Acceptance criteria
1. Not related	For cases where the criteria below do not apply
2. Related	Data clearly suggest a possibility of reasonable causal relationship between Synfolium and adverse events

6.A.(5).3).(b) Malfunctions

There were no reports of malfunctions with Synfolium during the evaluation period.

6.A.(6) Data for the long term after initial repair

In Study OFT-G1-301, a follow-up period was planned for 3-years after surgery. As of January 11, 2023, 100% (34 of 34) of subjects had completed a 2-year follow-up period after surgery and 17.6% (6 of 34) of subjects had completed the planned 3-year follow-up period after surgery.

During the period between 1 year and 3 years after surgery, pulmonary artery stenosis was reported as serious adverse event in 2 subjects, 1 of which had primary disease of tricuspid atresia as described above. Because pulmonary artery stenosis developed at a site different from the area where Synfolium was used, a causal relationship to Synfolium was denied. Percutaneous transluminal balloon angioplasty was performed 372 days after surgery, and the pulmonary artery stenosis resolved.

The other case of serious pulmonary artery stenosis occurred in a subject with tetralogy of Fallot. Pulmonary valve replacement with right ventricular outflow tract reconstruction was performed using Synfolium and a bioprosthetic valve ([redacted]), and many additional sutures were performed to stop bleeding. At the 2-year visit (733 days after surgery), although no symptoms were observed and echocardiography indicated “no” residual lesions, the subject was hospitalized to receive a protocol-unspecified examination of a cardiac catheterization before a transition period. Cardiac catheterization was performed at 735 days after surgery. Percutaneous transluminal balloon angioplasty was performed to repair the stenosis of the left pulmonary artery, which was found by the catheterization study, and the site was dilated without complications. The postoperative course was uneventful, and the subject was discharged from the hospital. The investigator determined a causal relationship of the event to Synfolium as “possibly related” and that a causal relationship of the event to the procedure as “related.”

6.B Outline of the review conducted by PMDA

6.B.(1) Clinical positioning of Synfolium

The applicant's explanation about the clinical positioning of Synfolium:

Gore-Tex EPTFE Patch II and Bovine Pericardial Patch are medical devices similar to Synfolium. Table 7 shows the comparison of indicated sites for Synfolium and these devices. The vessel walls to be indicated for Synfolium include the pulmonary artery (from the main pulmonary artery to the peripheral pulmonary artery), the major target site, as well as the aorta and the outer wall of the heart including the right ventricular outflow tract. The use of Synfolium will be limited to pediatric and adult patients with congenital heart disease (excluding pericardium).

Table 7. Indicated sites in comparison with similar medical devices

	Synfolium	Gore-Tex EPTFE Patch II	Bovine Pericardial Patch
Intended indication	Used for correction of blood flow, securing blood flow paths, and generation/reconstruction of surrounding tissues in congenital cardiac surgery	Used for repair of cardiac septum and outer wall of the heart, or pericardium. Used for repair or as a substitute for cerebral dura mater, or to prevent the surface of the brain from adhering to the dura mater or other subcutaneous tissue. However, the cardiac repair patch should only be used for the cardiac septum and outer wall of the heart.	Used for repair of the following sites or procedures. • Atrial septal defect • Ventricular septal defect • Femoral artery • Femoral vein • Right ventricular outflow tract • Mitral annuloplasty • Pericardial closure
Indicated site Indicated site for congenital heart disease	Cardiac septum Outer wall of the heart Vessel wall	Cardiac septum Outer wall of the heart Pericardium	Cardiac septum Right ventricular outflow tract Pericardium
Indicated site for non-congenital heart disease	(None)	Dura mater	Femoral artery Femoral vein Mitral annuloplasty

* Underlined tissue indicates the same tissue indicated for similar medical device(s)

As shown in Table 7, the detailed indications of Synfolium in congenital heart disease are similar, except for the repair of the pericardium, to those for conventional patches used for surgery. Study OFT-G1-301 confirmed that the clinical data are equivalent to those of similar medical devices, and showed that there are no adverse events unique to Synfolium or the adverse events are clinically acceptable. Because of its shape and structure (including raw materials), Synfolium can be used without impeding somatic growth. It consists of cells and components that compose the living blood vessel wall, and non-clinical studies showed formation of tissue containing vasa vasorum.

PMDA's view:

In accordance with its development concepts, the proposed indications of Synfolium in congenital heart disease are for the repair of the cardiac septum, outer wall of the heart, and vessel wall. The proposed indications are within the range of indications for already approved devices, and therefore there are no particular problems. The proposed indications do not include some conditions for which conventional patches have been used, such as traumatic injury other than congenital heart disease, ventricular aneurysm, aortic dissection, valve leaflet defect, left ventricular free-wall rupture, and there is no objection regarding its clinical positioning.

The development concepts of Synfolium were as follows: material is less prone to deterioration, restored to a condition that compares favorably with the function of living blood vessels without causing intima hyperplasia; and the ability to stretch as tissue grows. The advantages unique to Synfolium, i.e., extensibility to accommodate growth, reduction in calcification and other material deterioration, and prevention of stenosis caused by intima hyperplasia, have not been adequately evaluated for the following reasons: 1) although non-clinical study results have been obtained, it is difficult to extrapolate the animal study data to humans; 2) these advantages are difficult to evaluate within the limited time frame of a clinical study. Therefore, in the present evaluation, the clinical positioning of Synfolium should be evaluated as a patch for treating congenital heart disease in a manner equivalent to that used to evaluate conventional patches. Conversely, it is important to gather long-term data in the clinical practice to validate the development concepts of Synfolium.

6.B.(2) Appropriateness of using the submitted clinical study data for evaluation

6.B.(2).1) Appropriateness of study design

The applicant's explanation about the rationale for using data from Study OFT-G1-301 to evaluate the efficacy and safety of Synfolium and appropriateness of the primary endpoint and target performance:

Because Study OFT-G1-301 was the FIH study of Synfolium and Synfolium is an implantable study device used during surgery, as well as the feasibility of a clinical trial, the use of open-label and single-arm design was considered appropriate.

"The surgical success rate in the year following surgery" was selected as the primary endpoint. The rationale for the selection of the primary endpoint is as follows: Congenital heart disease, for which Synfolium is indicated, includes many types of structural anomalies, and the combination of anomalies is also complex. With the exception of some diseases, there is a scarcity of data from long-term outcome analyses conducted in a large number of patients. In addition, no clear evidence is available regarding the incidence of complications in the long term after initial

repair.[11] The clinical significance of Synfolium is that it can prevent death or reoperation occurring in the long term after initial repair by maintaining the sites reconstructed or repaired with Synfolium while securing safety after implantation. Furthermore, given that Synfolium is a device composed of non-biodegradable and biodegradable materials, 1 year was selected as the period after surgery that allows prediction of long-term efficacy and safety, when tissue reactivity caused by absorption reactions, etc. has stabilized. For Study OFT-G1-301, it was considered appropriate to select the surgical success rate in the year following surgery as a composite endpoint by which the efficacy and safety of Synfolium can be evaluated.

Conversely, for surgery and treatment of congenital heart disease, except for some mild diseases with a high rate of procedural success, patients require close monitoring and care in specialized medical institutions especially from childhood to adulthood,[11] and based on the specialists' information, long-term follow-up is provided in normal medical care. The duration of absorption of PLLA yarn used in Synfolium is [redacted] decided to follow patients for up to 3 years after surgery.

While Study OFT-G1-301 is an open-label, uncontrolled study, it is difficult to statistically demonstrate [redacted] when limited to surgery with difficulty level and follow-up period specified by the study. Therefore, taking into account the feasibility of a clinical trial, the sample size was calculated based on the clinical study data on the conventional patches. On the basis of the report[12] that [redacted], the expected success rate for Synfolium was assumed to be the same or higher, and [redacted]% was selected. In addition, [redacted]%, [redacted] patients [redacted] patients were specified.

To examine the clinical need for conventional patches and the performance required, a web-based questionnaire survey was conducted (February to March 2020) among cardiovascular surgeons and pediatric cardiologists with the cooperation of the Japanese Society of Pediatric Cardiology and Cardiac Surgery. The survey results revealed that freedom from reintervention (reoperation and catheter intervention) in augmentation/reconstruction of the right ventricular outflow tract to the pulmonary artery region was 80.2% in the 3-year period (2017 to 2020).[4] Given that this

questionnaire survey covered a wide range of diseases and surgical procedures, and that the freedom from reintervention was lower than that in the epidemiological survey data[13] used as reference when designing Study OFT-G1-301, the threshold of success rate [redacted]% specified for the study is considered appropriate and conservative. In the sample size design for Study OFT-G1-301, if [redacted] would be the same results. Therefore, it is considered that even [redacted] in Study OFT-G1-301 would not be clinically problematic.

Patient enrollment was controlled in an appropriate manner so that subjects who underwent right ventricular outflow tract reconstruction or pulmonary angioplasty using Synfolium accounted for ≥60% of the total. In addition, the investigator was instructed to enroll patients undergoing surgery in a low-pressure system. Because an uneven distribution of patients' conditions may affect factors such as the intended patient population at the time of approval and post-marketing safety measures, careful consideration was given to ensure that patients undergoing right ventricular outflow tract reconstruction or pulmonary angioplasty accounts for the majority of study patients, and that surgical procedures in a high-pressure system such as aortoplasty are always included.

PMDA's view:

The clinical positioning of Synfolium and its intended patient population are those with congenital heart disease requiring surgery; therefore, the single-arm study design evaluating the equivalence of Synfolium with conventional treatment methods is acceptable. Also, selecting "the surgical success rate in the year following surgery" as the primary endpoint is acceptable because its definition contains "death," "reoperation," and "reintervention," the clinical outcomes regarded as important for general surgery of congenital heart disease, and the outcomes for conventional treatment methods have been clear.

The results of the approved products indicate that it is difficult to statistically demonstrate the equivalence given the limited number of patients with congenital heart disease; therefore, it is acceptable to evaluate based on [redacted]. Consequently, the use of [redacted] resulted in [redacted], demonstrating the equivalence of Synfolium to conventional patches.

On the basis of the above and discussions from the Expert Discussion, PMDA concluded that it was acceptable to evaluate the efficacy and safety of Synfolium in a comprehensive manner based on the submitted clinical study results.

6.B.(2).2) Efficacy and safety of Synfolium

The applicant's explanation about the efficacy and safety of Synfolium:

In Study OFT-G1-301, "the surgical success rate in the year following surgery" was selected as the primary endpoint, and the point estimate was 100% (34 of 34) of subjects, with a 90% confidence interval of 91.6% to 100.0%. The lower limit of confidence interval exceeded the prescribed threshold of [redacted]%, and therefore the efficacy criteria of Synfolium predefined in the protocol were met. The safety data show that the incidence of adverse events was 88.2% (30 of 34) of subjects. The incidence of device-related adverse events was 11.8% (4 of 34) of subjects. These events were "pulmonary artery stenosis," "mediastinal haematoma," "pyrexia," and "post procedural haemorrhage" (1 subject each, 2.9%), none of which were rated as serious. The incidence of serious adverse events was 14.7% (5 of 34) of subjects. These events were "upper respiratory tract infection," atrial "tachycardia," "pulmonary artery stenosis," "pulmonary vein stenosis," and "post procedural haematoma" (1 subject each, 2.9%). There were no adverse events that led to death or study discontinuation. There were no reports on malfunctions of Synfolium during the evaluation period.

To compare the results of Study OFT-G1-301 with data on surgical outcomes for congenital heart disease in Japan, surgical outcome of procedures similar to those of Study OFT-G1-301 focusing on patches used in the clinical practice were comprehensively investigated. Finally, the applicant retrieved 5 reports with the outcome of patch angioplasty, mainly of the pulmonary artery. For the data from the 5 reports, the "freedom from reintervention" was calculated in addition to "death, reoperation, and reintervention," which are the primary endpoints of Study OFT-G1-301. While the follow-up period differs from that of Study OFT-G1-301 the results for the freedom from reintervention were 95.6%, 70.0%, 85.4%, 88.0%, and 96.5% for each report.[14,15,16,17,18] Similarly, the overseas outcome data were also investigated. These reports included the results of products not used in Japan, namely, CardioCel, PhotoFix, CorMatrix, homograft, and equine pericardial patch in addition to bovine pericardium used in Japan; however, the results were similar to those for Japan.[19,20,21,22,23,24,25,26,27]

The above findings demonstrate the efficacy and safety of Synfolium.

In relation to the results of the primary endpoint "the surgical success rate in the year following surgery," PMDA asked the applicant to explain in detail about the presence or absence of a causal relationship to Synfolium for the serious pulmonary artery stenosis occurred 6 days after surgery.

The applicant's explanation:

The diagram drawn by the investigator and findings at the time of reoperation indicated that the

major cause of the stenosis was the patient's own pulmonary artery being taut because the 18-mm diameter PTFE prosthetic vessel used in the Fontan procedure for this subject was slightly short. Therefore, stenosis was caused by a procedural problem unrelated to Synfolium.

PMDA concluded that the applicant's explanation is acceptable.

In another subject, a percutaneous transluminal balloon angioplasty was performed to treat the stenosis of the left pulmonary artery at 735 days after surgery. This stenosis was caused by many additional sutures performed to stop bleeding, and it was determined that there was a causal relationship to the procedure. PMDA asked the applicant to provide a detailed explanation regarding bleeding, safety of Synfolium, and precautions required for handling.

The applicant's explanation:
In Study OFT-G1-301, when confirming bleeding and hemostasis, in most cases, the subject's artery was grasped with forceps, and retracted towards the surgeon's side to expose the underlying tissue to allow the surgeon to look into the area. This stenosis was caused by damage to the gelatin layer by grasping the surface of the Synfolium patch with the forceps and pulling it towards the surgeon. To stop the bleeding, additional sutures were performed with suture thread alone or using autologous pericardium for reinforcement of the suture site, and bleeding was stopped by applying fibrin glue and the application of pressure. Regarding the difference in handling between Synfolium and conventional patches, the medical experts and investigator for Study OFT-G1-301 stated as follows: although Synfolium can be used with a procedure similar to that for conventional patches, it needs to be handled with care. After becoming familiar with the characteristics of Synfolium, a surgeon experienced in the procedure should not encounter difficulties in use. Therefore, risks can be managed by implementing the post-marketing safety measures discussed later.

On the basis of the discussions from the Expert Discussion, PMDA concluded that the difference between Synfolium and conventional patches in handling is acceptable by implementing the post-marketing safety measures discussed later.

On the basis of the above, PMDA concluded that the clinical efficacy and safety of Synfolium are acceptable because the prescribed target performance of Synfolium as equivalent to that of conventional patches has been demonstrated and there are no noteworthy safety-related events associated with Synfolium. However, given that the number of subjects studied was small and that Synfolium was not used in the aorta, a site which involves surgery in a high-pressure system, a problem which will be discussed later, careful decision-making will be required in order to

implement post-marketing safety measures.

6.B.(3) Post-marketing risk minimization measures

6.B.(3).1) Efficacy and safety when Synfolium is used in the aorta

In Study OFT-G1-301, Synfolium was implanted in the ventricular septum (11.8% [4 of 34] of subjects [4 sites]), the atrial septum (17.6% [6 of 34] of subjects [7 sites]), the pulmonary artery (50.0% [17 of 34] of subjects [18 sites]), and the right ventricular outflow tract (35.3% [12 of 34] of subjects [12 sites]). Synfolium was not used in the aorta. In the event of blood leak, the risk is considered to be greater in the aorta than the atrial septum, and considering the differential pressure, pressure is higher in the aorta than in the ventricular septum. PMDA asked the applicant to explain the appropriateness of including the aorta in the indications.

The applicant's explanation:

- Very few patients undergo implantation in the aorta. Given the number of subject enrolled, a possibility had been foreseen that no subjects would undergo implantation in the aorta.
- As for blood leak, under the test pressure of 16 kPa (120 mmHg) specified in ISO 7198:2016 (Cardiovascular implants and extracorporeal systems–Vascular prostheses–Tubular vascular grafts and vascular patches), the volume of water leak was [redacted] g/min for Synfolium, meeting the acceptance criteria of [redacted] g/min. The standard value in the same test was <1.0 mL/cm^2/min for Triplex, a vascular prosthesis graft that can be used in the aorta (Approval No. 21900BZY00013000). The value is equivalent to [redacted] g/min for the test device used in the permeability study of Synfolium, indicating that the volume of water leak for Synfolium is less than the standard value for Triplex.
- In the study of implantation in an animal vessel wall and the study of long-term implantation in the vessel wall of dogs, Synfolium was implanted in the thoracic descending aorta. At [redacted], [redacted], and [redacted] years after implantation, there have been no reports of morphological anomalies (e.g., rupture and aneurysmal change), which is considered to occur when the wall cannot withstand high pressure. When a load of [redacted] under the physiological conditions was mechanically applied to tissue pieces from the implanted site of Synfolium at [redacted], and [redacted] years after implantation, no break was observed at the implanted site, indicating that the stress resistance to pressure was higher than that of the animal's own artery wall.
- While no patients underwent implantation of Synfolium in the aorta in Study OFT-G1-301, 1 patient underwent implantation of Synfolium in a vessel wall that is subjected to relatively high blood pressure. This was a subject with pulmonary atresia with a complication of the major aortopulmonary collateral artery (MAPCA), which is known to have a high pulmonary arterial pressure. Synfolium was used for pulmonary angioplasty and the pulmonary arterial pressure was approximately 70% of the aortic pressure. The investigator noted no particular

intraoperative blood loss, and there were no adverse events on the implanted site that raised safety concerns.

- Of [redacted] animals studied so far, a prototype, which is knitted more densely than Synfolium, was used in [redacted] animals, and Synfolium was used in [redacted] animals. Of [redacted] animals, Synfolium was implanted in the descending aorta in [redacted] animals, including [redacted] animals in which Synfolium is still implanted. No development of aneurysm or rupture occurred during the maximum period of [redacted] years.
- In reference data, Synfolium was implanted in the inferior vena cava in a dog, and balloon dilation was performed at [redacted] and [redacted] months after implantation to treat procedure-related stenosis. The balloon dilation was successful and no anomalies were found during the subsequent period.
- The results of histological observation over time show the time-course change of in situ tissue regeneration at the implanted site of Synfolium in the descending aorta (Figure 4).[28,29]
  - In the early-stage after implantation, reactions of general fibrous tissue are observed (characterized by the absence of agglomeration of inflammatory cells).
  - By [redacted] months after implantation, the cross-linked gelatin that coated the fabric has gradually disappeared, and tissue infiltrated the space between the fibers (at this time, the process of endothelial cells lining the luminal surface has completed).
  - As PLLA yarn disappears, the space in the residual PET yarn expands over time, forming wall-penetrating tissue containing vasa vasorum (it is considered that this establishes nutrient supply to newly forming intimal tissue, preventing abnormal thickening and securing adhesion to PET yarn).
  - Throughout the period between [redacted] to [redacted] years after implantation, the tissue structure remained stable without change.

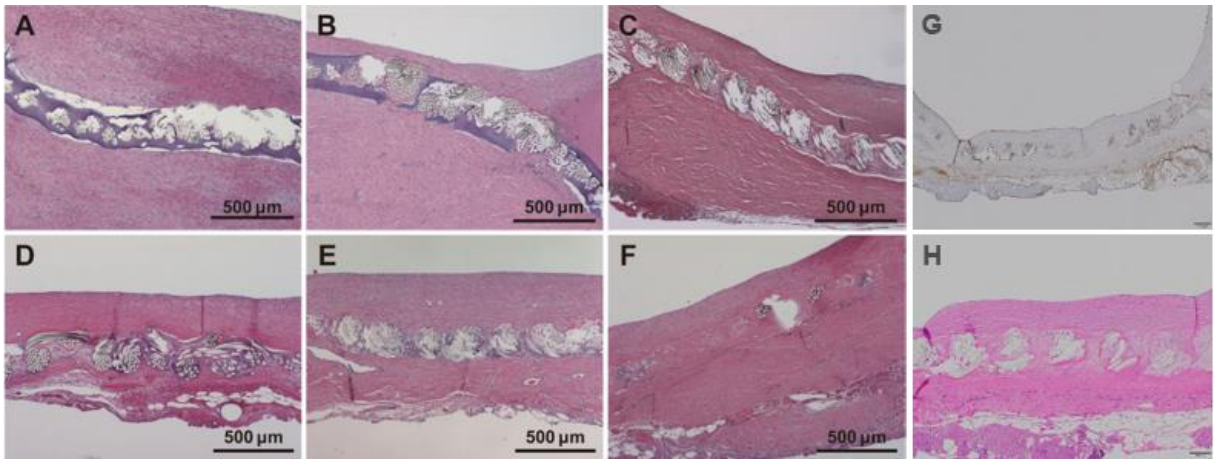

Figure 4. Time-course change after implantation in the aortic wall (A, [redacted]; B, [redacted]; C, [redacted]; D, [redacted]; E, [redacted]; F, [redacted]; G, [redacted] [von Willebrand Factor (vWF) staining]; and H, [redacted]. Hematoxylin Eosin [HE] staining except for G. Topmost edge in the photographs is the luminal side)

- Of the 34 subjects in Study OFT-G1-301, 2 subjects developed a stenotic lesion during the follow-up period up until November 29, 2022, and percutaneous transluminal balloon angioplasty was performed. Both balloon angioplasty procedures were successful with favorable recovery.

Non-clinical evaluation data of Synfolium in the aorta can provide all the information needed for clinical use, and there are no particular concerns. Taking account of the comments from the Expert Discussion, PMDA concluded not to exclude the aorta from the indication of Synfolium. After the product launch, the institutions that can use Synfolium in the aorta should be limited until data are accrued from the use-results survey over a specified period and evaluated. Then, institutions that can use Synfolium in the aorta should be gradually added.

6.B.(3).2) Efficacy and safety of Synfolium when sutured directly to other materials

Taking account of the comments from the Expert Discussion, PMDA considered that the following efficacy and safety issues could raise concerns when Synfolium is sutured directly to other materials such as Gore-Tex EPTFE Patch II, and asked the applicant to explain the following issues.

(a) Rupture and bleeding at suture site in the long term after initial repair
(b) Strength at the suture site depending on the stitching method in the long term after initial repair
(c) Possibility of regression earlier compared with conventional treatment
(d) Possibility that regenerative tissue detaches easily from Synfolium

(e) Safety of performing balloon dilation when stenosis develops in the suture site

The applicant's response:

- In Study OFT-G1-301, Synfolium was sutured directly to other materials in 11 of 34 subjects (32.4%): PTFE artificial vessel was sutured to Synfolium used for pulmonary artery augmentation (3 subjects); Synfolium was directly implanted on the sewing cuff of the bioprosthetic valve (7 subjects); PTFE 0.1 mm was sewn to Synfolium as leaflets and used as a single-valved patch for pulmonary angioplasty (1 subject). All 11 subjects completed the 2-year follow-up. The residual lesions status as determined by echocardiography and the incidence of adverse events indicate no particular problems in the areas where Synfolium was sutured directly to other materials.
- The physical properties (tensile strength, suture retention strength, pinhole leak) of Synfolium are similar to those of Gore-Tex EPTFE Patch II and Bovine Pericardial Patch.[29] Therefore, it is unlikely that when Synfolium is sutured directly to conventional materials, Synfolium would cause morphological changes to the material or vice versa. In general situations, the possibility that the suture technique (e.g., patch trimming, continuous sutures, interrupted sutures) or the type of surgical suture could change the integrity of condition (deformation and stenosis at the suture site) of Synfolium is similar to that for conventional materials. The risk of rupture of Synfolium or conventional materials caused by suturing is unlikely to occur under normal use.
- Figure 5 shows the knitted structure of Synfolium. The photograph on the right shows [redacted]. While this is not unique to suturing of different materials, it is difficult to selectively suture the PLLA yarn area only.

Figure 5. Photographs of knitted structure.
(Actual size [left]; [redacted] magnifications [middle]; [redacted] magnifications [right])

- The patch implantation of Synfolium in the descending aorta in the dog showed layered continuous transition between the native vessel wall and regenerative tissue at the suture site, and the finding is histologically consistent.

- Because Synfolium forms a vessel wall that has a typical histological structure supported by adequate strength and self-generated tissue repair, it is unlikely that Synfolium causes interactions (Synfolium provokes deterioration of conventional materials, or vice versa) with other materials when it is sutured to conventional materials.

PMDA's view on the efficacy and safety of Synfolium when sutured directly to different materials:
The implantation of Synfolium in the descending aorta in the dog showed layered continuous transition between the native vessel wall and regenerative tissue at the suture site, and the finding is histologically consistent. It is also difficult to confine suturing to solely the area of biodegradable PLLA yarn because of the fine knitted structure. In Study OFT-G1-301 and animal studies, there were no events attributable to the suture method. In addition, Synfolium was sutured directly to a different material in 11 subjects in Study OFT-G1-301, and no problems were reported at the suture site. Therefore, PMDA concluded that it is not necessary to exclude direct suturing of Synfolium to other materials from the indications based on the applicant's explanation and comments from the Expert Discussion. The applicant should continue to collect long-term data on subjects enrolled in Study OFT-G1-301, and data including results from the use-results study should be promptly provided to healthcare professionals when new findings become available.

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

As described earlier, physicians' subjective impression of operability was evaluated as a secondary endpoint in Study OFT-G1-301. For each operability item, the sum of ratings 5, 4, and 3 (5 = excellent, 4 = good, and 3 = fair) were as follows : ease of cutting, 94.1% (32 of 34) of subjects; ease of needle/thread penetration, 97.1% (33 of 34) of subjects; resistance to fraying, 91.2% (31 of 34) of subjects; compatibility with tissue, 82.4% (28 of 34) of subjects; and degree of blood leak after implantation, 67.6% (23 of 34) of subjects.

PMDA asked the applicant to explain how precautionary information on trimming and needle handling would be provided based on the evaluation results:

The applicant's response:
It is considered that no special training is necessary before introducing Synfolium, and precautions will be provided in the package insert. The package insert will include the "Precautions Concerning Usage" section to provide cautionary statements on the precautions for cutting and notes on needle handling.

When introducing the product into each medical institution, information will be provided to physicians at information sessions and workshops for healthcare professionals before use of the product begins. Table 8 summarizes the information to be provided at the sessions.

Synfolium is formed with a cross-linked gelatin film. Like other conventional patches, if the patch is grasped too firmly with forceps or other instruments, the patch may be damaged, which may cause bleeding. The patch must be handled gently, and therefore, a cautionary statement will be included in the package insert. Furthermore, while the appearance and texture of Synfolium are similar to those of autologous pericardium, a biological tissue, its physical properties (feeling of resistance when stretching) differ from those of an autologous pericardium. If the same needle handling technique as that used for autologous pericardium is adopted, gaps may be formed; therefore, the needle must be manipulated carefully to prevent the formation of gaps between Synfolium and the patient's own tissue.

Table 8. Information to be provided to healthcare professionals

Item	Details
Overview of product	• Explanation of Synfolium in accordance with the package insert, such as the intended use • Show the results of the clinical trial and examples of events involving suture handling* that occurred during the clinical trial * The following will be explained regarding suture handling: • Causes of bleeding that occurred in the clinical trial (e.g., operation procedure) and how to respond when bleeding occurs • Share experts' and investigator's tips and advice when using Synfolium
Suture practice	• Prepare artificial skin, surgical suture, needle, scissors, needle holder, clamps, forceps, tweezers, etc. and sample of Synfolium. Physicians will practice techniques from trimming to suturing. • Staff near the desk will follow up and advise if physician is not confident about procedures. • Intentionally grasp the gelatin film firmly with forceps or scratch the surface of the gelatin film to demonstrate how the gelatin film can be damaged.

The applicant explained that Synfolium does not differ significantly from the approved products from an operational perspective, and PMDA accepts that no special training is necessary. However, PMDA considers that the applicant should provide detailed notes and other information to healthcare professionals.

6.B.(5) Intended use

On the basis of the above discussion, PMDA concluded that the intended use should be as follows to clarify the target patient population:

Intended use or indication

Synfolium is used for correction of blood flow, securing blood flow paths, and generation/reconstruction of surrounding tissues in congenital cardiac surgery.

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

7.A Summary of the data submitted

Table 9 shows the summary of the use-results survey (draft) presented by the applicant for the present application.

Table 9. Summary of use-results survey (draft)

Item	Details
Population	Patients who undergo congenital cardiac surgery for correction of blood flow, securing blood flow paths, and generation/reconstruction of surrounding tissues (Patients in whom Synfolium is to be sutured to any of the following: ventricular septum, atrial septum, right ventricular outflow tract, pulmonary artery, and aorta)
Planned sample size	150 patients (all patients in whom Synfolium is used in the aorta [≥10 patients])
Rationale	In this use-results survey, "surgical success rate at 5 years after surgery"* was selected as the key analysis item to evaluate the efficacy and safety of Synfolium in clinical practice. The incidence of reintervention including death was set to 4.0%, using data on reoperation, etc. reported for conventional treatment methods as reference. A sample size of 150 will allow the detection of ≥1 case at a probability of ≥99%, taking into account a drop-out rate of 20%. * There should be no deaths or reintervention (reoperation, balloon dilation) for which a causal relationship to Synfolium cannot be ruled out. Reintervention does not include pharmacotherapy.
Survey period	7 years (preparation for marketing and registration period, 1 year and 6 months; follow-up period, 5 years; analysis, 6 months)
Key survey item	Presence/absence of reintervention at the implanted site of Synfolium

It was decided that institutions that can use Synfolium in the aorta after the product launch will be specified in the proper use guidelines prepared by the Japanese Society of Pediatric Cardiology and Cardiac Surgery. Whether to add institutions that can use Synfolium in the aorta will be decided based on the data collected in the year following surgery from the use-results survey, as well as data collected over the 3 years when a number of assessments on safety in the clinical practice are expected to be obtained.

Apart from the use-results survey, the applicant plans to collect information from Japanese study patients who sign the additional informed consent regarding the presence/absence of reintervention up to 5 years after surgery, occurrence of death, and serious adverse events. In cooperation with the relevant academic societies, the applicant also plans to gather data from patients who completed the use-results survey for up to 10 years after surgery, which is the general timeframe for clinical literature.

7.B Outline of the review conducted by PMDA

Taking account of the comments from the Expert Discussion, PMDA concluded that the applicant

should collect information on patients who have undergone cardiac surgery using Synfolium to evaluate safety and efficacy, as well as efficacy and safety data from patients in whom Synfolium has been used in the aorta, which were not obtained in Study OFT-G1-301. Additional risk minimization measures should also be taken as necessary.

The use of Synfolium in the aorta should be started at the use results survey sites under contract, because Synfolium has not been used clinically in the aorta even though non-clinical data cover the entire evaluable range of use. The applicant explained that whether to add the institutions that can use Synfolium in the aorta will be considered in cooperation with the academic societies and a decision will be made around 3 years later, when there will be a number of assessments regarding safety in clinical practice. PMDA concluded that the applicant's explanation is acceptable.

On the basis of the above, PMDA concluded that the applicant's plan for the use-results survey is appropriate and decided to include the use-results survey as an approval condition.

8. Documents Relating to Information on Precautions, etc. Specified in Paragraph 1 of Article 63-2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, in Relation to Notification Pursuant to the Same Paragraph of the Act

8.A Summary of the data submitted

The applicant submitted Information on Instructions for use (labeling) (draft) as an attachment in accordance with the Notification titled "Application for Marketing Approval of Medical Devices" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, as described earlier in Section "6.B. Outline of the review conducted by PMDA," PMDA concluded that there were no particular problems with the proposed Instructions for use (labeling), provided that the applicant advises necessary caution.

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

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

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

and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

When conducting its review, PMDA primarily focused on (1) the efficacy and safety of Synfolium and (2) post-marketing safety measures. PMDA reached the following conclusions, taking account of deliberations at the Expert Discussion:

(1) Efficacy and safety of Synfolium

Currently available clinical data on Synfolium are similar to those on conventional patches; therefore, the efficacy and safety are clinically acceptable. The development concepts of Synfolium were as follows: material is less prone to deterioration, restored to a condition that compares favorably with the function of living blood vessels without causing intima hyperplasia; and the ability to stretch as tissue grows. While some of these aspects have been evaluated in non-clinical studies, long-term clinical data need to be gathered. It is important to gather not only data from the use-results survey but also longer-term clinical data in cooperation with the relevant academic societies, and provide information to the healthcare professionals.

(2) Post-marketing safety measures

Although no patients in Study OFT-G1-301 underwent implantation of Synfolium in the aorta, the artery that must be able to withstand the greatest blood pressure, it was decided not to exclude the aorta from the indication of Synfolium because there were no adverse events that could raise safety concerns in subjects undergoing implantation on the vessel wall subjected to relatively high blood pressure, and findings including tissue regeneration have been observed in Synfolium implanted in the canine descending aortic wall. However, the institutions that can use Synfolium in the aorta after the product launch should be limited until data accrued from the use-results survey over a specified period can be evaluated, in accordance with the proper use guidelines created in cooperation with the relevant academic societies, and thereafter, institutions that can use Synfolium in the aorta should be gradually added in stages.

Synfolium is a device developed in Japan, and both clinical study data and long-term data are limited. Accordingly, the applicant should gather information on the intended patient population, reintervention rates, and adverse events through the use-results survey; examine the clinical data on Synfolium based on the post-marketing safety measures; and take additional risk minimization measures. The follow-up period should be 5 years, the survey period for the use- results survey should be 7 years (preparation for marketing and registration period, 1 year and 6 months; follow-

up period, 5 years; analysis, 6 months), and all patients in whom Synfolium is used in the aorta should be included in the use-results survey (Approval Condition 2).

In addition to the data from the use-results survey, the applicant should assess the long-term safety data from Study OFT-G1-301, conducted earlier and take additional risk minimization measures if necessary (Approval Condition 1).

As a result of the above review, PMDA has concluded that Synfolium may be approved with the following intended use (modified from the proposed text) and approval conditions.

Intended Use

Synfolium is used for correction of blood flow, securing blood flow paths, and generation/reconstruction of surrounding tissues in congenital cardiac surgery.

Approval Conditions

1. The applicant is required to submit the results of interannual analyses of long-term prognosis data from participants in the clinical study for marketing approval to the Pharmaceuticals and Medical Devices Agency and to take appropriate measures as necessary.
2. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product in the aorta, in accordance with the proper use guidelines prepared in cooperation with the relevant academic societies, and to submit to the Pharmaceuticals and Medical Devices Agency the results of interannual analyses of long-term prognosis while taking appropriate measures as necessary.

The product is designated as a medical device subject to a use-results survey, and the use-results survey period should be 7 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.

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