February 22, 2013
Office of Medical Device Evaluation
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Medical products 4, Orthopedic products
Term Name	Collagen-containing absorbable nerve regeneration inducing material
Brand Name	Nerve Regeneration Guidance Conduit Nerbridge
Applicant	Toyobo Co., Ltd.
Date of Application	February 29, 2012 (Application for marketing approval)

Results of Deliberation

In its meeting held on February 22, 2013, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product should be approved with a re-examination period of 3 years. The product is classified as a specially controlled medical device and is not classified as a specially designated maintenance-and-management-required medical device, a biological product, or a specified biological product.

Review Report

January 30, 2013
Pharmaceuticals and Medical Devices Agency

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

Classification	Medical products 4, Orthopedic products
Term Name	Collagen-containing absorbable nerve regeneration inducing material (to be newly created)
Brand Name	Nerve Regeneration Guidance Conduit Nerbridge
Applicant	Toyobo Co., Ltd.
Date of Application	February 29, 2012 (Application for marketing approval of medical device)
Reviewing Office	Office of Medical Devices II

Review Results

January 30, 2013

Classification	Medical products 4, Orthopedic products
Term Name	Collagen-containing absorbable nerve regeneration inducing material (to be newly created)
Brand Name	Nerve Regeneration Guidance Conduit Nerbridge
Applicant	Toyobo Co., Ltd.
Date of Application	February 29, 2012 (Application for marketing approval of medical device)

Results of Review

Nerve Regeneration Guidance Conduit Nerbridge (hereinafter referred to as "Nerbridge") is a polyglycolic acid conduit filled with sponge-like collagen. Nerbridge is intended to be used to bridge a gap between the stumps of the peripheral nerve that has been severed or damaged due to traumatic injury or other causes, thereby inducing regeneration of the damaged nerve and restoring its function.

The applicant submitted the results from non-clinical studies on physicochemical properties, biological safety, *in vivo* biological safety of tin compounds, decomposition and absorption, intramuscular implantation, and sciatic nerve repair, and results from pathology of the tissue surrounding the peripheral nerve injury repaired with Nerbridge. No particular problem was identified during the review.

The applicant submitted the clinical data from a multicenter clinical study of Nerbridge conducted in Japan (at 20 study sites). The study evaluated Nerbridge in the treatment of patients with a severed peripheral nerve with a defect ≥2 mm at the distal wrist, in comparison with autologous nerve graft. The primary endpoint of the study was the result of a sensory function test by the Semmes-Weinstein method (SW test) at 36 weeks postoperative. The study was conducted to demonstrate the non-inferiority of Nerbridge to the control procedure. For safety analysis, all the adverse events were monitored to evaluate the incidence of adverse events (malfunctions) for which a causal relationship to Nerbridge or autologous nerve graft could not be ruled out. This clinical study was initiated as a randomized, controlled study. However, patient enrollment did not progress as planned because study subjects had to be randomly assigned to either Nerbridge or autologous nerve graft. For this reason, the study design was changed to a non-randomized design in the course of the study. As a result, 60 subjects were included in the Nerbridge group as of the completion of the study, while only 6 subjects were enrolled in the control group. Each result of the SW sensory test, the primary endpoint, was rated on a 3-point scale (excellent, good, and poor). In the Nerbridge group, the result was rated as excellent for 22 subjects (37.9%), good for 26 subjects (44.8%), and poor for 10 subjects (17.2%). Overall, 48 subjects (82.8%) had a rating of excellent or good. In contrast, in the control group, the result was rated as excellent for 2 subjects (33.3%), good for 2 subjects (33.3%), and poor for 2 subjects (33.3%).

Overall, 4 subjects (66.7%) had a rating of excellent or good. The secondary endpoints were the results of sensory function tests by the static and dynamic 2-point discrimination method at 36 weeks postoperative. In the Nerbridge group, the result of a static 2-point discrimination test was rated as excellent for 15 subjects, good for 23 subjects, and poor for 19 subjects. Overall, 38 subjects (66.7%) had a rating of excellent or good. In contrast, in the control group, the result was rated as excellent for 2 subjects, good for 4 subjects, and poor for 0 subjects. Overall, 6 subjects (100%) had a rating of excellent or good. In the Nerbridge group, the result of a dynamic 2-point discrimination test was rated as excellent for 17 subjects, good for 16 subjects, and poor for 24 subjects. Overall, 33 subjects (57.9%) had a rating of excellent or good. In contrast, in the control group, the result was rated as excellent for 1 subject, good for 3 subjects, and poor for 2 subjects. Overall, 4 subjects (66.7%) had a rating of excellent or good. Safety analyses revealed adverse events reported in 35 subjects (58.3%) in the Nerbridge group and 4 subjects (66.7%) in the control group. Malfunctions considered to be causally related to Nerbridge or autologous nerve graft were reported in 6 subjects (10%) (infection in 4 subjects, device deviation in 2 subjects) in the Nerbridge group and 3 subjects (50.0%) (anesthesia, hypoesthesia, and numbness at the nerve harvest site in 1 subject each) in the control group. None of these malfunctions were serious. Because of the limited sample size of the control group in this clinical study, the applicant also submitted data on autologous nerve graft from a foreign clinical study of a similar medical device, retrospective investigations at the study sites, and literature search. The submitted data have confirmed that autologous nerve graft is not common in this patient population in clinical practice, while the outcome of neurorrhaphy or conservative therapies is poor, though they are commonly performed in clinical settings. Based on these findings and the results of the retrospective investigations at the study sites and literature search, it is of significance to make Nerbridge available to patients and healthcare professionals.

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

Intended Use

Nerbridge is intended to be used to bridge a gap between the stumps of the peripheral nerve that has been severed or damaged due to traumatic injury or other causes, thereby inducing regeneration of the nerve and restoring its function (except for peripheral nerves in the dura mater).

Review Report

January 30, 2013

I. Product for Review

Classification	Medical products 4, Orthopedic products
Term Name	Collagen-containing absorbable nerve regeneration inducing material (to be newly created)
Brand Name	Nerve Regeneration Guidance Conduit Nerbridge
Applicant	Toyobo Co., Ltd.
Date of Application	February 29, 2012 (Application for marketing approval of medical device)
Proposed Intended Use	Nerve Regeneration Guidance Conduit Nerbridge is used to promote the reconstruction of a damaged nerve and improve its function in patients with an acute, subacute, or old peripheral nerve defect or disease.

II. Product Overview

Nerbridge is a polyglycolic acid (PGA) conduit filled with sponge-like collagen. The conduit is intended to be used to bridge a gap between the stumps of the peripheral nerve that has been severed or damaged due to traumatic injury or other causes, thereby inducing regeneration of the nerve and restoring its function. The outer surface of the conduit is also covered with collagen, and the device itself is absorbed and decomposed in the body in several months, which are usually required for the nerves to be reconstructed (Figures 1 and 2).

To use Nerbridge, the proximal and distal stumps of a svered nerve need to be freshly resected for better nerve regeneration. After an appropriate size of the Nerbridge conduit is selected, each nerve stump is inserted several millimeters into the end of the conduit, and then sutured to the conduit.

Fig. 1. Outline of treatment with Nerbridge

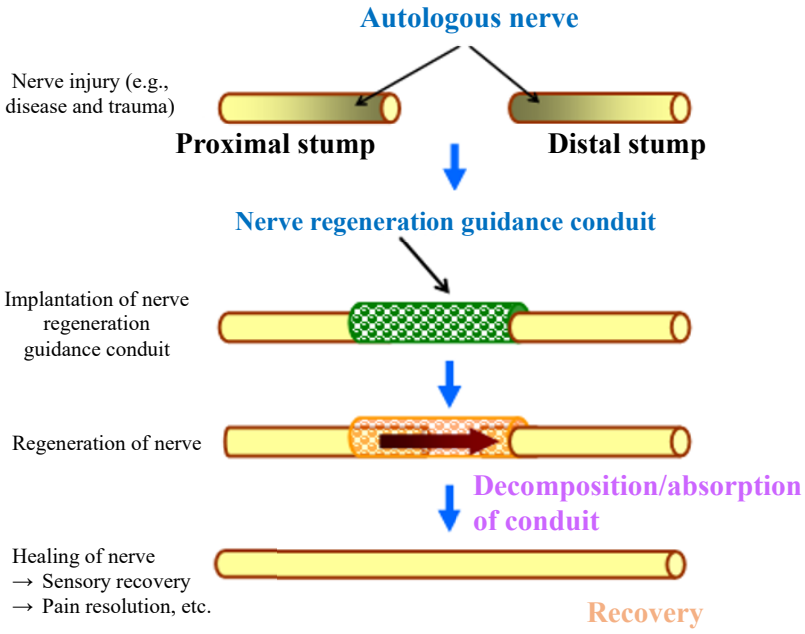

Fig. 2. Exterior appearance of Nerbridge

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

The data submitted for the present application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. The expert advisors present during the Expert Discussion on Nerbridge declared that they did not fall under Item 5 of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

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

Origin or history of discovery

End-to-end nerve suture is performed under a microscope to repair severed peripheral nerves due to traumatic injuries, diseases, or other causes. When the crushed segment of a nerve needs to be resected and removed or when extensive removal of a malignant tumor leaves a significant nerve defect, autologous nerve grafting is indicated because end-to-end nerve suture creates tension in the sutured nerve segment, resulting in a poor treatment outcome. Autologous nerve grafting, however, has the following drawbacks: (i) It requires harvesting of a donor nerve, and the donor source is limited to the sensory nerves, such as the sural nerve and the cutaneous nerve of the forearm, where resection causes less severe postoperative dysfunction; there is also a limit on their quantities; (ii) autologous nerve grafting is highly invasive, requiring the sacrifice of a healthy nerve; and (iii) the surgical procedures are cumbersome, requiring a long surgical and anesthetic time. For these reasons, artificial materials that could replace autografts are demanded.

With recent advances in research on peripheral nerve regeneration, requirements for auxiliary materials for nerve coaptation (materials that are used to repair a nerve defect) necessary for nerve regeneration have been clarified. While axons are elongating or regenerating to form a fascicle, the auxiliary material must prevent the connective tissue from ingrowing, must allow for substance exchange between the inside and outside of the material, must serve as a scaffold suitable for Schwann cell growth and axon regeneration, and must be absorbed and decomposed in the body during nerve regeneration so that they do not inhibit nerve regeneration or cause inflammation or strangulation. In 1975, the Institute for Frontier Medical Sciences, Kyoto University focused on the biocompatibility of collagen and started experiments with molded conduits made of collagen. Around the early 1980's, experiments on these conduits applied to animal sciatic or other nerves achieved a certain degree of success. Based on these experiments, collagen was selected as the scaffold. Around 1995, a nerve regeneration guidance conduit filled with collagen was developed. The conduit was made of PGA, a nerve coaptation auxiliary material, which had long been used in absorbable sutures, etc. Animal experiments of this conduit in cats, dogs, and monkeys demonstrated successful peripheral nerve reconstruction. In 2003, the Institute for Frontier Medical Sciences, Kyoto University requested the applicant to put the above nerve regeneration guidance conduit into production. In 2004, the applicant started the development of the product for commercialization.

Overseas, Neurotube (made of PGA), a marketed device to which Nerbridge is considered substantially equivalent, achieved FDA 510k clearance in 1999. Since then, the following devices have been marketed: NeuroGen (approved in 2001, type I collagen), Neuroflex (approved in 2001, type I collagen), NeuroMatrix (approved in 2001, type I collagen), AxoGaurd (approved in 2003, porcine small intestinal submucosa), and Neurolac (approved in 2005, polylactic acid and ε-caprolactam). These devices are used for regeneration of not only damaged peripheral nerves in the hand but also damaged lower extremity nerves and craniocervical nerves, including facial nerves. Allografts that have been treated by decellularization or other methods are also commercially available.

Use and malfunctions in foreign countries

Nerbridge has not been approved, marketed, or used in foreign countries.

Malfunctions reported overseas with similar devices include infection and device protrusion.

2. Setting of Specifications

Neither official standards nor guidelines that can be referred to in setting the specifications for Nerbridge are available. Therefore, in view of the specifications for an approved bioabsorbable artificial dura mater (Seamdura, 21900BZZ00040000), made of copolymers of L-lactide with ε-caprolactam and PGA, as well as of the characteristics of Nerbridge, the specifications for Nerbridge included the following tests: appearance before absorption, tension strength, and decomposition to evaluate strength and morphological stability during absorption. In addition, requirements for sterilization (sterility assurance level, ethylene oxide sterilization residuals, and sterility tests), biological safety tests, and other safety tests, such as bacterial endotoxins, were included in the specifications. The specification limits of these tests were specified based on the target performance

values determined as design requirements and the results of design verification. The quality and safety of porcine dermis-derived collagen are described later in Section "7. Manufacturing Process."

PMDA reviewed the justification for the proposed specification tests and limits, and accepted them.

3. Stability and Durability

To support the stability and durability of Nerbridge, the applicant submitted the results of the tests on appearance, size, tension strength, decomposition, infrared absorption spectroscopy, nuclear magnetic resonance spectroscopy, and bacterial endotoxins. These tests used samples stored in real time for [redacted] years ([redacted]°C) at the time of submitting the application. None of the tests revealed any particular problem. The shelf-life of 2 years at 1°C to 30°C was determined. PMDA asked the applicant to explain why the results of the test samples stored at [redacted]°C justify the storage of Nerbridge at 1°C to 30°C.

The applicant's explanation:

The applicant additionally submitted the results of the same tests using test samples stored in real time for [redacted] years ([redacted]°C). The results of these tests justified the above storage condition because they showed no problems.

Based on the above results, PMDA concluded that the shelf-life of 2 years was appropriate.

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

The applicant submitted a declaration of conformity declaring that Nerbridge meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act (hereinafter referred to as "the Essential Principles") (MHLW Public Notice No. 122 of 2005) and the Ministerial Ordinance on Quality Management System for Medical Devices and *In Vitro* Diagnostics (MHLW Ministerial Ordinance No.169 of 2004).

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

5. Performance

5.a. Physicochemical properties

To support the physicochemical properties of Nerbridge, the applicant submitted the results of the tests on appearance, dimension, tension strength, tearing strength, compression strength, decomposition, bacterial endotoxins, and sterility among the tests in the specifications. None of the tests revealed any particular problem.

PMDA reviewed the submitted physicochemical data and accepted them.

5.b. Biological safety

Nerbridge is coapted to the nerve tissue and implanted in the body. Nerbridge itself is decomposed and absorbed in the body, and disappears. In accordance with ISO 10993-1, the following tests required for implants that come into contact with tissue or bone for a long period of time were conducted using Nerbridge: Cytotoxicity, skin sensitization, reverse mutation, chromosomal aberration, short-term intramuscular implantation (1 month), long-term intramuscular implantation (3 months), acute systemic toxicity, intradermal reaction, pyrogenicity, and hemolytic toxicity tests. The results of the tests were all negative, without any particular problem.

The manufacturing of polyglycolic acid (PGA), a raw material of Nerbridge, requires an organotin compound (tin di [2-ethylhexanoate]) as a catalyst. In addition to the above biological safety tests which are generally included in the specifications, data on residual tin compounds in Nerbridge determined by [redacted] were submitted at the time of submission of the application.

The applicant's explanation about the data:
The maximum weight of the organotin compound that can be contained in 1 conduit (Nerbridge) is estimated to be [redacted] μg, based on the obtained tin content. This figure is substantially lower than the oral toxicity dose reported with organotin compounds and their degradation products.[1)] The use of several Nerbridge conduits is even acceptable from the toxicological viewpoint. Many *in vivo* tests have shown no genotoxicity of mono- and di-alkyltin. Dibutyltin diacetate is reportedly not carcinogenic in rats or mice.[2)] The neurotoxicity of organotin compounds is likely to occur not by direct contact with the nerves but in the process of absorption, metabolism, or excretion.[3),4)] Organotin compounds are already used, as additives for raw materials of medical devices, in greater amounts than those in Nerbridge. These findings and knowledge indicate the substantially low risk of neurotoxicity of Nerbridge. In light of their physical properties, organotin compounds are very unlikely to convert to highly toxic compounds in the manufacturing process of Nerbridge.

With reference to the applicant's explanation that the neurotoxicity of organotin compounds does not occur by direct contact with the nerves, PMDA asked the applicant to explain whether the toxicological risk of Nerbridge which directly come into contact with the nerves was sufficiently investigated.

The applicant's explanation:
The applicant additionally submitted the results of a histological and ultrastructural study in which Nerbridge was used for nerve regeneration in a rabbit model of nerve transection injury. Most of the area surrounding the implanted test sample had a very mild degeneration of the nerve fibers without any demyelinating change. There were axonal regeneration changes, which indicate the ongoing repair process of the severed nerve. These findings suggest no abnormality in the regeneration process of the nerve tissue replaced by Nerbridge.

PMDA accepted the applicant's response.

5.c. Studies on decomposition and absorption

The applicant submitted the results of a test that verifies the biodegradation behavior and safety of Nerbridge. In this test, Nerbridge was placed subcutaneously in rabbits, and the condition of the implant remaining in the body and inflammatory reactions of the surrounding tissue were investigated after a certain period of time. Gross observation of Nerbridge in the body revealed the clear remains of the implant at 14 days post-implantation, no clear trace of the implant at 44 days post-implantation, and the absence of the implant at 64 days post-implantation. At any time point, gross observation showed no obvious inflammatory reaction or redness in the surrounding tissue of the implantation site. Pathology of the test samples at 14 days post-implantation revealed cell growth and neovascularization, suggesting no adverse effect on the surrounding tissue or nerve regeneration. In summary, Nerbridge was decomposed and absorbed in the body in approximately 3 months, without causing any safety problem at the implantation site.

PMDA asked the applicant to conduct a biological safety test of degradation products that form in the process of decomposition and absorption of Nerbridge in the body.

The applicant's response:

Polyglycolic acid, which is an absorbable material used in Nerbridge, has long been used in absorbable sutures. This material is hydrolyzed in the body to form low-molecular weight oligomers and glycolic acid. Glycolic acid and low-molecular weight oligomers are carried to the kidneys or liver via the blood flow and eliminated from the body in urine or feces.[5),6),7)] Alternatively, glycolic acid is decomposed to glycine and oxalic acid, and finally to water and carbon dioxide via the citric acid metabolic pathway.

PMDA accepted the above applicant's response because the only other degradation product is a tin compound used as a catalyst, whose toxicity has already been investigated and explained by the applicant.

5.d. Studies on sciatic nerve repair

The applicant submitted gross observation and pathological data from a study that investigated the nerve reconstruction with Nerbridge and the reconstruction process in a rabbit model of sciatic nerve resection injury. Gross observation and pathology were performed after a certain period of time following the implantation of Nerbridge in the animal model. Gross observation of the test samples at >72 days post-implantation showed complete decomposition and absorption of Nerbridge, resulting in disappearance from the body. On the other hand, the test samples remained in the body at 24 days post-implantation, with the nerve extending from the proximal end of the Nerbridge conduit. Pathology revealed findings suggesting the phagocytosis of the remaining test samples by phagocytes at 56 days post-implantation, with only mild histiocytic infiltration in the test samples at 72 days post-implantation. The test samples at 115 days post-implantation showed the presence of nerve fibers suggesting nerve regeneration, with most of the remaining test samples being absorbed in the body. Based on the above, the applicant explained that Nerbridge guided the regeneration of the severed peripheral nerves only causing mild reaction at the implantation site, and that Nerbridge can be used safely.

PMDA accepted the applicant's explanation.

6. Risk Analysis

The applicant submitted the company regulations regarding risk management that comply with JIS T 14971:2003, as well as documents on the risk management system and its implementation status. (The applicant submitted a summary of the risk management, risk management system, and its implementation status for Nerbridge, in accordance with ISO 14971 "Medical devices - Application of risk management to medical devices.") Hazards against which safety measures were requested by the Ministry of Health, Labour and Welfare or foreign governmental agencies etc. with respect to Nerbridge and similar devices have not been reported to date.

PMDA reviewed the submitted data on risk analysis and accepted them.

7. Manufacturing Process

Quality and safety of biological ingredients

The applicant's explanation about the quality and safety of the collagen (derived from porcine dermis) used in Nerbridge, and the pepsin (derived from porcine stomach mucosa), [redacted] used in the manufacturing of the collagen:

All of these ingredients have been shown to be derived from healthy animals. Information required to assure their quality and safety is recorded and retained. Of the ingredients, [redacted] falls under (1) "Biological ingredients and materials scientifically known to have no risk of infection with bacteria or virus" specified in 3. Standards for animal-derived ingredients, 4. General rules for animal-derived ingredients, the Standards for Biological Ingredients (MHLW Public Notice No. 210 of 2003). The collagen, pepsin, and [redacted] are subjected to alkali treatment (pH 13, [redacted]) and virus inactivation by [redacted] ([redacted]) in their manufacturing processes. The manufacturing process of Nerbridge also includes inactivation of pathogens by [redacted] ([redacted]). [redacted] are [redacted], respectively. They meet the criteria specified in 1. Standards for ruminant-derived ingredients, 4. General rules for animal-derived ingredients, the Standards for Biological Ingredients.

On the basis of the above explanation by the applicant, PMDA has concluded that the biological ingredients used as raw materials of Nerbridge meet the Standards for Biological Ingredients, and that their quality and safety are assured.

Manufacturing process, sterilization, and quality control

The applicant submitted information on the manufacturing process and manufacturing facilities, sterilization method (ethylene oxide sterilization), and quality control.

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

8. Clinical Data

The applicant submitted clinical data from a multicenter clinical study conducted in Japan (the Japanese clinical study). The applicant also submitted the following reference data to support the analysis of the data from the Japanese clinical study: Published data from the control groups in a foreign clinical study of a similar medical device; clinical data from patients who previously underwent autologous nerve grafting at the 20 study sites that participated in the Japanese clinical study; and clinical data on autologous nerve grafting in the literature.

Clinical study

(1) Study plan

The Japanese clinical study was a prospective clinical study in patients with a severed peripheral nerve at the distal wrist to evaluate the efficacy and safety of Nerbridge versus autologous nerve graft. Originally, this clinical study was initiated in a randomized, assessor-blinded, controlled design with the planned sample size of 110 (55 per group) at 5 study sites. The key inclusion criteria included the age (≥15 and <65 years) at informed consent, a nerve defect of ≥2 and ≤40 mm, a nerve width of ≤4 mm, and either an acute or old nerve defect (old nerve defect within 2 years after the initial surgery).

The primary efficacy endpoint was the result of a sensory function test by the Semmes-Weinstein method (SW test) at 36 weeks postoperative (Week 36). The secondary endpoints were the results of static and dynamic sensory function tests by the 2-point discrimination method at Week 36. The objective of the Japanese clinical study was to demonstrate the non-inferiority of Nerbridge to autologous nerve graft (control) using the non-inferiority margin of −20%). The efficacy was analyzed using full analysis set (FAS) and per protocol set (PPS). The FAS was used for the primary efficacy analysis. Table 1 shows the acceptance criteria of each test.

Table 1. Efficacy acceptance criteria

Test	Excellent	Good	Poor
SW test[*1] (unit, Fm[*2])	Normal = 1.65-2.83 Diminished light tough = 3.22-3.61	Diminished protective sensation = 3.84-4.31	Loss of protective sensation = 4.56-6.65
Static 2-point discrimination[*3]	≤6.0 mm	7.0-15.0 mm	≥16.0 mm
Dynamic 2-point discrimination[*3]	≤4.0 mm	5.0-7.0 mm	≥8.0 mm

*1 SW test: Apply each of the nylon monofilaments of different sizes slowly at a perpendicular angle to the test area of the skin. Apply force until the filament bends. Determine whether the patient can feel the force.
*2 Fm: Filament marking. The force (gw) applied on each filament is log-transformed.
*3 Two-point discrimination test: Apply each of the 2-point discrimination testing devices of different intervals to the skin to measure the shortest distance between the caliper tips at which the patient perceives 2 distinct stimuli.

All the adverse events were monitored and safety analyses were performed based on the incidence of adverse events (malfunctions) for which a causal relationship to Nerbridge or autologous nerve graft could not be ruled out.

(2) Study results

The Japanese clinical study was conducted from December 2007 to March 2011. Because of a substantial delay in subject enrollment, the study design was changed from the randomized design to a non-randomized design in [redacted] 20[redacted]. The number of study sites was increased to 20. This clinical study eventually enrolled 60 subjects in the Nerbridge group and 6 subjects in the control group.

Of 66 enrolled subjects (60 in the Nerbridge group, 6 in the control group), 64 subjects (58 in the Nerbridge group, 6 in the control group) were included in the FAS and 60 subjects (54 in the Nerbridge group, 6 in the control group) in the PPS. No statistical analysis was performed because of the limited sample size of the control group.

Tables 2 and 3 show the results of the primary and secondary efficacy endpoints, respectively. One subject in the FAS missed a Week 36 visit. In the analysis of the primary endpoint of this subject, the result at Week 24 was used according to the Last Observational Carried Forward (LOCF) method (using the last available result), as defined in the statistical analysis plan. This subject was excluded from the analysis of the secondary endpoints because the statistical analysis plan does not specify any relevant rule.

Table 2. Primary endpoint: Results of sensory function test by SW method (Week 36) (FAS)

		Excellent	Good	Poor	Excellent or good
Nerbridge	Number of subjects	22	26	10	48
	%	37.9%	44.8%	17.2%	82.8%
Control	Number of subjects	2	2	2	4
	%	33.3%	33.3%	33.3%	66.7%

Table 3. Secondary endpoints: Results of static and dynamic sensory function tests by 2-point discrimination method (Week 36) (FAS)

		Excellent	Good	Poor	Excellent or good (improvement rate)
Static	Nerbridge	15	23	19	38 (66.7%)
	Control	2	4	0	6 (100.0%)
Dynamic	Nerbridge	17	16	24	33 (57.9%)
	Control	1	3	2	4 (66.7%)

Major factors that may affect the efficacy are the length of the nerve defect, the width of the nerve defect, and the time from injury to surgery. Stratified analyses by these factors were performed (Table 4). Although no statistical analysis could be performed in any strata because of the limited number of subjects, the results suggested a certain level of the efficacy of Nerbridge, regardless of the length of the nerve defect, the width of the nerve defect, and the time from injury to surgery.

Table 4. Stratified analysis: Results of sensory function test by SW method (Week 36) (FAS)

		Group	Excellent	Good	Poor	Excellent or good (improvement rate)
Length of nerve defect	2 to <10 mm	Nerbridge	7	4	4	11 (73.3%)
		Control	2	1	2	3 (60.0%)
	10 to <20 mm	Nerbridge	11	11	5	22 (81.5%)
		Control		1		1 (100.0%)
	20 to <30 mm	Nerbridge	2	8	1	10 (90.9%)
		Control				-
	30-40 mm	Nerbridge	2	3		5 (100.0%)
		Control				-
Width of nerve defect	<1 mm	Nerbridge	4	2	2	6 (75.0%)
		Control	1			1 (100.0%)
	1 to <2 mm	Nerbridge	10	12	4	22 (84.6%)
		Control	1	2		3 (100.0%)
	2 to <3 mm	Nerbridge	8	10	4	18 (81.8%)
		Control			2	0 (0.0%)
	3-4 mm	Nerbridge		2		2 (100.0%)
		Control				-
Time from injury to surgery	<1 day	Nerbridge	5	8	4	13 (76.5%)
		Control				-
	1-3 days	Nerbridge	3	1	2	4 (66.7%)
		Control		1		1 (100.0%)
	4 to <30 days	Nerbridge	7	10	1	17 (94.4%)
		Control	1		1	1 (50.0%)
	≥30 days	Nerbridge	6	8	3	14 (82.4%)
		Control	1	1	1	2 (66.7%)

Table 5 shows a list of malfunctions, as a result of safety evaluation. Adverse events occurred in 35 of 60 subjects (58.3%) in the Nerbridge group. Malfunctions considered to be causally related to Nerbridge occurred in 6 subjects (10.0%, 7 malfunctions). Adverse events occurred in 4 of 6 subjects (66.7%) in the control group. Malfunctions considered to be causally related to the control procedure occurred in 3 subjects (50.0%).

Table 5. List of malfunctions

Malfunctions	Nerbridge (N = 60)			Control (N = 6)		
	Number of malfunctions	Incidence	Outcome	Number of malfunctions	Incidence	Outcome
Postoperative wound infection	4	6.7%	Resolving	0	0.0%	
Device expulsion (accompanied by infection)	1	1.7%	Resolving after device removal	0	0.0%	
Wound tunneling	1	1.7%	Resolving after device removal	0	0.0%	
Nausea	1	1.7%	Resolving	0	0.0%	
Hypoesthesia/anesthesia at denervated site	0	0.0%		2	33.3%	No healing
Numbness of heel	0	0.0%		1	16.7%	Resolving

Serious adverse events were reported in 3 subjects (3 events) in the Nerbridge group. A causal relationship to Nerbridge was ruled out for all events (Table 6).

Table 6. List of serious adverse events in the Nerbridge group

Age	Sex	Adverse event	Date of surgery	Date of onset	Outcome	Causal relationship to Nerbridge
49	Male	Necrosis of left middle finger	[redacted]	[redacted] Day 0	Resolving	Unrelated (due to ischemia, no vascular compression by Nerbridge)
52	Female	Right carpal tunnel syndrome	[redacted]	[redacted] Day 101	Recovery	Unrelated (due to other causes such as frequent use of hand)
34	Male	Acute appendicitis	[redacted]	[redacted] Day 91	Recovery	Unrelated (accidental event, resolved while the device was in use)

Other data

To complement data from the control, which only enrolled a limited number of subjects (N = 6), the applicant submitted the following reference data: Published data from the control group in a US clinical study of a similar medical device; clinical data from patients who previously underwent autologous nerve grafting at the 20 study sites that participated in the Japanese clinical study; and clinical data on autologous nerve grafting in the literature.

(a) Published data from the control group in US clinical study of similar medical device

The applicant submitted published data on autologous nerve grafting in a clinical study of Neurotube, a medical device to which Nerbridge is considered substantially equivalent. The data were available from the US FDA and used as a historical control (Table 7). This study included a control group of 46 cases. Only 7 fingers (including 6 fingers of 1 subject) were treated by autologous nerve grafting at the distal wrist, as in the control group of the Japanese clinical study. The remaining 39 fingers underwent other nerve repair procedures including end-to-end suture. The primary endpoint of this study was the improvement rate at Month 12 as determined by the 2-point discrimination tests. This was different from the primary endpoint of the improvement rate at Week 36 based on the SW test in the Japanese clinical study. The rating of the static 2-point discrimination test was good in 6 fingers (85.7%) with a mean distance of 13.8 mm. The rating of the dynamic 2-point discrimination test was poor in 6 fingers (85.7%) with a mean distance of 12.5 mm.

Table 7. Clinical outcome in subjects who underwent autologous nerve grafting, extracted from published information on Neurotube (7 fingers)

Subject No.	Finger	Site	2-point discrimination (Month 12) (mm)	
			Static	Dynamic
51	Thumb	Radial side	11 (good)	8 (poor)
51	Index finger	Radial side	14 (good)	13 (poor)
51	Middle finger	Radial side	15 (good)	13 (poor)
51	Annular finger	Ulnar side	13 (good)	11 (poor)
51	Little finger	Radial side	15 (good)	15 (poor)
51	Little finger	Ulnar side	15 (good)	15 (poor)
82	Thumb	Ulnar side	(Followed only up to Month 6)	(Followed only up to Month 6)
Mean			13.8	12.5

(b) Clinical data from patients who previously underwent autologous nerve grafting at 20 study sites that participated in Japanese clinical study

Only 4 subjects received autologous nerve grafts at the distal wrist, as in the control group of the Japanese clinical study, and were followed up over a similar period of time (Table 8). The rating over

the follow-up period of 7.5 to 15.7 months (mean, 11.5 months) was excellent in 1 subject (25%) and good in 3 subjects (75%), with a mean Fm of 3.92.

Table 8. Clinical outcome in subjects who underwent autologous nerve graft at 20 study sites (N = 4)

[redacted]	[redacted]	Finger	Site	Fm (SW test) (rating)	Follow-up period
[redacted]	[redacted]	Left little finger	Ulnar side	3.22 (excellent)	10.9 months
[redacted]	[redacted]	Left thumb	Radial side	4.31 (good)	15.7 months
[redacted]	[redacted]	Right index finger	Radial side	4.31 (good)	7.5 months
[redacted]	[redacted]	Left annular finger	Ulnar side	3.84 (good)	11.8 months
Mean				3.92	11.5 months

(c) Literature, etc.

The applicant submitted literature data on autologous nerve grafting in 15 fingers of 12 subjects. The results of SW tests over the follow-up period of 10 to 36 months (mean, 15.1 months) were 3.84 to 4.31 (good) in all patients.[8)]

Table 9 shows the clinical outcome in the control group of the Japanese clinical study. As aforementioned, the rating of the SW test, the primary endpoint, was excellent in 2 subjects (33.3%), good in 2 subjects (33.3%), and poor in 2 subjects (33.3%), with a mean Fm of 4.06. The rating of the static 2-point discrimination test, a secondary endpoint, was excellent in 2 subjects (33.3%) and good in 4 subjects (66.7%), with a mean distance of 7.8 mm. The rating of the dynamic 2-point discrimination test, another secondary endpoint, was excellent in 1 subject (16.7%), good in 3 subjects (50.0%), and poor in 2 subjects (33.3%), with a mean distance of 6.0 mm.

Table 9. Clinical outcome in the control group of the Japanese clinical study (Month 9)

Finger	Fm (SW test) (rating)	2-point discrimination (mm) (rating)	
		Static	Dynamic
Left middle finger	2.83 (excellent)	8 (good)	5 (good)
Left annular finger	4.56 (poor)	9 (good)	9 (poor)
Left annular finger	4.31 (good)	6 (excellent)	5 (good)
Left annular finger	4.31 (good)	7 (good)	7 (good)
Left annular finger	5.88 (poor)	15 (good)	8 (poor)
Left thumb	2.44 (excellent)	2 (excellent)	2 (excellent)
Mean	4.06	7.8	6.0

The limited sample sizes of these studies, as well as the differences in the primary endpoint and the duration of the follow-up period among the studies, preclude a simple comparison. However, the outcome of autologous nerve grafting did not substantially differ between the control group of the Japanese clinical study and the historical control data, indicating that results of comparison with the historical control data are similar to the outcome of evaluation of Nerbridge versus control in the Japanese clinical study.

PMDA asked for the applicant's opinions on the following issues:

(1) Whether the efficacy and safety of Nerbridge can be evaluated based on the results of the Japanese clinical study, which enrolled only 6 subjects in the control group.

(2) Whether it is justified that the application site of Nerbridge is not specified, despite the results of the Japanese clinical study which enrolled only patients with a severed peripheral nerve at the distal wrist. Whether Nerbridge can be applied to peripheral nerves in the dura mater.
(3) Precautions for use of Nerbridge. Device protrusion has been reported overseas with similar devices. The applicant needs to explain about the implantation of Nerbridge into the nerve adjacent to the joint, the use of Nerbridge in patients with severe soft tissue injury, and postoperative therapy under such conditions.
(4) Long-term efficacy and safety

The applicant's responses:

(1) Whether the efficacy and safety of Nerbridge can be evaluated based on the results of the Japanese clinical study

The Japanese clinical study was originally designed as a randomized, controlled study because it was considered necessary to compare the study results of Nerbridge with those of autologous nerve graft, the most effective conventional treatment for patients with a large nerve defect. However, patient enrollment did not progress as expected, for the following reasons: (i) Autologous nerve grafting, which involves harvesting of a donor nerve, causes several problems, such as nerve function loss, pain, and numbness at denervated sites, and aesthetic problems (new wound); and (ii) treatment outcome is easily influenced by operation time, prolonged anesthesia time, and surgeon's skills. Randomization was inevitably renounced, resulting in the small sample size of the control group. Since it was considered difficult to evaluate the efficacy and safety of Nerbridge based only on the results of the Japanese clinical study, data collection from the control group in a foreign clinical study of a similar medical device, retrospective investigations in patients who underwent autologous nerve grafting at the study sites, and literature search were performed. The data included a certain number of patients who received autologous nerve grafts. As aforementioned, however, only small number of patients were qualified in terms of the endpoint and follow-up period when the data were matched based on the patient characteristics; namely 4 patients who previously underwent autologous nerve grafting at the study sites and 7 patients who underwent autologous nerve grafting, extracted from published information from the foreign clinical study of Neurotube. Despite the limited sample size, the outcome in these patients did not substantially differ from the outcome in subjects receiving autologous nerve graft in the Japanese clinical study. It is possible to compare the results in the Nerbridge group with the numerical data from 6 subjects in the control group in the Japanese clinical study. Sufficient historical control data could not be collected for the following reasons: 1) Autologous nerve graft itself is not very common; 2) some patients lost to postoperative follow-up (compliance issue); and 3) postoperative sensory function tests were not performed or not documented in medical records.

For a reference on the current situation of conventional treatment of severed nerves (including nerves without a defect), the proportion of treatment procedures performed in the last 3 years at the study sites, etc. was investigated. The investigation identified autologous nerve grafting in 25 patients, neurorrhaphy in 678 patients, and conservation therapy (no treatment) in 60 patients. A total of 14 patients had a nerve defect ≥2 mm and underwent neurorrhaphy at these study sites. The treatment outcome in these patients was excellent in 1 patient, good in 2 patients, and poor in 11 patients.

Although neurorrhaphy is commonly performed, end-to-end suture for a nerve with a defect beyond a certain length may put excessive tension on the nerve creating a gap at the suture site, thus allowing scar tissue ingrowth. The scar tissue ingrowth hinders nerve regeneration, blocks the blood flow to promote fibrosis, and causes other problems, resulting in a poor nerve reconstruction, which often leaves pain and numbness. In addition, nerve suturing with the joint excessively flexed may cause joint contracture or loss of nerve gliding, which causes adhesion, and the traction of the severed nerve during joint movements, which inhibits axon regeneration. Surgeon's skills can also considerably influence treatment outcome.[10)-15)] Millesi et al. conducted fundamental and clinical research. They reported that the contraction of scar tissue damaged the regenerating axons, causing axonal degeneration and that this phenomenon was clearly correlated with the degree of the tension at the suture site. They concluded that the tension at the suture site is the key factor that has the largest impact on the outcome of neurorrhaphy. This finding has been widely accepted.[16)] In summary, neurorrhaphy is known to have its limits in treating large nerve defects.

Nerbridge is intended to be used in the treatment of severed nerves, classified as Grade V nerve injury according to the Sunderland Classification.[9)] Grade V nerve injuries mean macroscopic evidence of complete disruption of a nerve. Grade V nerve injury is defined as the "disruption such that spontaneous nerve regeneration is unlikely to occur and recovery cannot be achieved without surgical intervention." These definitions are widely accepted. Conservation therapy is not expected to resolve sensory loss or intractable pain associated with painful neuroma of amputation stump. In the Japanese clinical study, 2 subjects with intractable neuropathic pain due to a severed nerve prior to the operation achieved improvement in pain after the treatment with Nerbridge, suggesting that Nerbridge is effective in not only preventing but also treating neuropathic pain.

Although autologous nerve grafting is considered to be the most suitable for the treatment of large nerve defects, it is not commonly performed for the reasons mentioned above. Neurorrhaphy or conservation therapy is more common, but such procedure often fails to provide sufficient recovery. Because autologous nerve grafting requires a relatively long operative time and some technical challenges, it is more common to first repair the bone, blood vessel, tendon, etc. during the primary surgery, and then perform autologous nerve grafting during the secondary surgery. Introduction of Nerbridge to clinical practice will allow for nerve reconstruction during the primary surgery, which will be beneficial for patients because it reduces their mental and physical burdens.

(2) Application sites

In the Japanese clinical study, patients with a nerve defect (maximum length, 40 mm; maximum diameter, 4 mm) at the distal wrist were treated with Nerbridge, and the results demonstrated a certain level of the efficacy of Nerbridge. Peripheral nerves other than those in the distal wrist contain motor nerve fibers. However, peripheral nerves in any region have nerve fibers consisting of axons and surrounding Schwann cells. Nerve fibers are collected into fascicles covered by the perineurium. These nerve fascicles are covered by the epineurium. Given these points, all peripheral nerves are anatomically and developmentally the same regardless of the regions. Their neurophysiological characteristics, including spike transmission, degeneration, and regeneration, are also the same among the peripheral nerves. Nerbridge is, therefore, expected to provide a similar efficacy to that seen in the

Japanese clinical study in the treatment of damaged peripheral nerves in any region other than the distal wrist. Autologous nerve grafting in clinical practice involves transplant of the sural nerve, which is a sensory nerve in the lower limbs, to reconstruct a facial nerve as a motor nerve. Treatment outcome with similar devices in the forearm median nerve, ulnar nerve,[17),18)] brachial plexus,[19)] lower limb nerves,[20)] facial nerves,[21)] and cerebral nerves, including the accessory nerve,[22)] has been reported overseas. These publications reported a good recovery of motor function without a noteworthy adverse event.

In summary, Nerbridge can be applied to peripheral nerves in regions that were not assessed in the Japanese clinical study. However, peripheral nerves in the dura mater should be excluded from the intended use, because the safety of Nerbridge has not been verified for use in the dura mater where the device may come into contact with the cerebrospinal fluid or central nerve.

(3) Precautions for use of Nerbridge

No adverse events such as the protrusion of Nerbridge were reported in the Japanese clinical study. However, there were no investigation on the implantation of Nerbridge into the nerve adjacent to the joint, detailed rules for postoperative therapy, assessment of associated soft tissue injuries, or evaluation of postoperative joint range of motion. The safety of Nerbridge under such conditions remains unknown. Soft tissue injuries accompanying nerve defects vary from patient to patient, and therefore it is not practical to apply a uniform definition of soft tissue injuries. Treatment for soft tissue injuries depends on the physician's diagnosis. Device protrusion (a malfunction) reported in the literature control data is likely to have occurred because soft tissue injury prevented the device from being completely covered.[23),24)] On the basis of the above, Nerbridge should be carefully implanted for reconstruction of the peripheral nerve adjacent to the joint and appropriate rehabilitation should be performed for patients who underwent such procedure. Nerbridge should not be used in patients who are at high risk of wound infection because of severe wound contamination or patients with a severe soft tissue loss. These precautions should be included in the instructions for use. The method of use should include the description to the effect that "physicians and healthcare professionals must start rehabilitation after external fixation at least 1 week postoperative, comprehensively considering the positional relationship between the application site of Nerbridge and the adjacent joint, and the recovery status of the soft tissue of the surrounding bone." In addition, seminars should be held during the meetings of relevant academic societies, etc. as needed to provide information about the proper use of Nerbridge. The surgical procedures for the implantation of Nerbridge are not particularly difficult compared with those for autologous nerve grafting. Nevertheless, Nerbridge should ideally be used by surgeons who are used to manipulating fine nerves. A precautionary statement to the effect that "Nerbridge should be used properly by surgeons with sufficient knowledge and experience of nerve reconstruction" should be included in the instruction for use to reduce the risks.

(4) Long-term efficacy and safety

The follow-up period of the Japanese clinical study was 36 weeks postoperative. Common malfunctions reported in this clinical study were infection and device protrusion, which occurred in the relatively early postoperative phase. The published data from long-term follow-up (covering several postoperative years) of patients who received similar devices overseas showed no malfunctions

specific to the long-term use of the device or compromised effectiveness in terms of sensory or motor function during the prolonged use.[17),18),25)] A review by Mermans et al. in 2012 showed a positive correlation between the duration of follow-up and the recovery of sensory function.[26)] Nerbridge is bioabsorbable, and is absorbed and decomposed in the body in several months. Malfunctions, such as trapped nerve which has been reported in clinical research of nonabsorbable materials, cannot occur theoretically.[27)]

PMDA's view on the applicant's response:

(1) The investigation conducted by the applicant and other information has suggested that severed peripheral nerves with a defect ≥2 mm, the medical condition targeted in the Japanese clinical study, are commonly treated by neurorrhaphy or conservation therapy (no treatment) because of the invasiveness, cumbersome procedures, and other problems of autologous nerve grafting. It is understandable to change the design of the Japanese clinical study to the non-randomized design. The control group in the submitted Japanese clinical study enrolled only 6 subjects. Because of this limited sample size, the clinical study failed to demonstrate a statistically significant superiority of Nerbridge to conventional treatments in terms of efficacy and safety. There are limits in evaluating the efficacy and safety of Nerbridge based on the results of the Japanese clinical study alone. However, the results of the SW test, the primary endpoint, showed treatment effectiveness in 82.8% of the subjects in the Nerbridge group versus 66.7% of the subjects in the control group. Even 2 subjects with intractable neuropathic pain associated with nerve severance, which often requires chronic pain management with analgesics, had improvement in pain after the treatment with Nerbridge. In addition, foreign publications, etc. have reported the efficacy and safety of medical devices to which Nerbridge is substantially equivalent.[17)-26)] Given these points, Nerbridge appears to have a certain level of efficacy. The applicant explained that the literature data also demonstrated a better treatment outcome with Nerbridge than neurorrhaphy or conservation therapy (no treatment), which are more common in the target patient population of Nerbridge, in clinical practice. This applicant's explanation is largely accepted.

Nerbridge has not been associated with significant safety issues. However, most of the target patient population of Nerbridge will have an open wound, which may increase the risk of infection. Postoperative wound infection, which was classified as a moderate malfunction, was observed in 4 subjects (6.7%) in the Nerbridge group. Relevant information, precautions, etc. should be provided to healthcare professionals using the instructions for use in order to ensure that eligible patients are selected. Although adverse events associated with harvesting of a donor nerve, such as hypoesthesia, anesthesia, and numbness at the donor nerve site, were observed in 3 subjects (50%) in the control group, those adverse events cannot occur with Nerbridge. This could be a significant advantage of Nerbridge.

In summary, the Japanese clinical study demonstrated a certain level of efficacy and safety of Nerbridge. The treatment procedures currently performed in clinical practice have many associated problems. Nerbridge is expected to solve these problems to some extent. PMDA has concluded that it is of clinical significance to make Nerbridge available to patients and healthcare professionals in clinical practice as a new treatment option.

(2) In the Japanese clinical study, reconstruction of the sensory nerve was only assessed in treating a severed peripheral nerve at the distal wrist. A severed peripheral nerve can occur not only in the above region but also anywhere (e.g., the forearm, upper arm, neck, face, and lower limbs). The only differences between the peripheral nerves in these regions and those in the target region of this clinical study are their diameter and the presence of motor nerves. For the following reasons, PMDA considered it possible to extrapolate the results of the Japanese clinical study to patients with a severed peripheral nerve in any body region:

- Nerbridge comes in 8 different inner diameters from 0.5 to 4.0 mm in 0.5-mm increments, with a length of 55 mm. In the Japanese clinical study, Nerbridge was used in nerve defects of 2 to 40 mm in length and 0.4 to 3.5 mm in width. The stratified analysis showed no substantial difference in treatment outcome among the defects in this range of length or width. The size variation of Nerbridge appears to be sufficient to achieve sensory nerve reconstruction to a certain extent.
- Treatment outcomes with similar devices in the forearm median nerve, ulnar nerve, brachial plexus, facial nerves, and cerebral nerves, including the accessory nerve, have been reported overseas. These publications showed a good recovery of motor function without a noteworthy adverse event.[17)-26)]
- The US FDA has imposed no restrictions on areas or nerves for which similar devices marketed in the US are indicated. Those devices have successfully been used in peripheral nerves all over the body. No noteworthy issue has been identified in the US FDA adverse event reporting.
- In clinical practice, autologous nerve grafting is performed using a sensory nerve to reconstruct a motor nerve, with some efficacy.
- Nerbridge is used to guide the regeneration of severed peripheral nerves. In that sense, there is no substantial developmental, anatomical, or neurophysiological difference between motor and sensory nerves. Nerbridge, which has been shown to be effective in sensory nerves, can therefore be expected to have a similar efficacy in motor nerves.

On the basis of the above discussion, the applicant's explanation that the efficacy and safety results of the Japanese clinical study can be extrapolated to peripheral nerves in any body region that was not investigated in this clinical study is reasonable to a certain extent. However, the efficacy and safety of Nerbridge in the treatment of nerves with a defect >40 mm have not been verified in the study. Information about this fact should be provided to healthcare professionals. In addition, a use-results survey involving a certain proportion of patients with severed motor nerves treated with Nerbridge should be conducted so that the efficacy of Nerbridge in motor nerve reconstruction can be appropriately evaluated based on manual muscle testing, electromyogram, etc. and that the safety of Nerbridge can be evaluated in detail. Reconstruction of motor nerves may require more time than that of sensory nerves. PMDA instructed the applicant to collect long-term data. The applicant agreed. As explained by the applicant, peripheral nerves in the dura mater should be excluded from the intended use, because the safety of Nerbridge has not been verified for use in the dura mater where the device may come into contact with the cerebrospinal fluid or central nerve.

(3) Although no protrusion of Nerbridge was reported in the Japanese clinical study, considering the overseas reports on similar devices,[23),24)] the applicant decided that the instructions for use should include precautionary statements to the effect that Nerbridge should be carefully implanted for reconstruction of the peripheral nerve adjacent to the joint and appropriate rehabilitation should be performed for patients who underwent such procedure and that Nerbridge should not be used in patients who are at high risk of wound infection because of severe wound contamination or patients with a severe soft tissue loss. PMDA accepted the applicant's decision. The surgical procedures to implant Nerbridge are relatively easier and less cumbersome than those for autologous nerve grafting. Considering the conditions under which Nerbridge will be used (i.e., surgeons and medical institutions), no other particular requirements are needed for those surgeons or medical institutions. Nevertheless, the following applicant's explanation is reasonable: The instructions for use should include the precautionary statement to the effect that "Nerbridge should be used properly by surgeons with sufficient knowledge and experience of nerve reconstruction" to reduce the risks.

(4) The long-term outcome of treatment with Nerbridge was not fully evaluated in the Japanese clinical study. As explained by the applicant, however, the common malfunctions in the Japanese clinical study occurred in a relatively early stage after the procedure and the long-term results of similar devices overseas showed neither malfunctions specific to long-term treatment nor efficacy concerns.[17),18),25)] On the basis of these findings, there are no significant concerns about the long-term outcome after nerve regeneration with Nerbridge. Nevertheless, as described in (2) above, PMDA instructed the applicant to collect long-term data from patients with motor nerve regeneration through a post-marketing surveillance because reconstruction of motor nerves may require more time than that of sensory nerves.

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

Results of document-based compliance inspection

The new medical device application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Pharmaceutical Affairs Act. 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.

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

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

V. Overall Evaluation

Nerbridge is intended to be used to bridge a gap between the stumps of the peripheral nerve that has been severed or damaged due to nerve severance or other causes, thereby inducing regeneration of the nerve. PMDA's review of the application for Nerbridge focused on (1) whether the efficacy and safety of Nerbridge can be evaluated based on the results of the submitted clinical study; (2) whether

Nerbridge can be applied to regions that were not investigated in the clinical study; (3) the precautions for use of Nerbridge; and (4) the long-term efficacy and safety of Nerbridge.

PMDA's conclusions reached taking account of discussions on the Expert Discussion:

(1) For the following reasons, it is of significance to make Nerbridge available to patients and healthcare professionals in clinical practice: (a) Although the use of autologous nerve graft is considered for patients with a large nerve defect, these cases are commonly treated by neurorrhaphy or left untreated in clinical practice because of the invasiveness, cumbersomeness, and other drawbacks of autologous nerve grafting; (b) the publications, etc. clearly show the poor treatment outcome in patients with a large nerve defect who underwent neurorrhaphy or left untreated; (c) Nerbridge is beneficial in that the sacrifice of a healthy nerve is avoided, unlike in the case of autologous nerve grafting, and the clinical study did not demonstrate a clearly inferior outcome with Nerbridge to autologous nerve graft although no statistical analysis could be performed to verify the non-inferiority of Nerbridge; and (d) similar devices have already been used successfully and established as an treatment option overseas.

(2) The clinical study was conducted in patients with a severed or damaged nerve at the distal wrist. There are some differences between the distal wrist and other regions. The other regions (a) have large nerves, which can be associated with longer nerve defects, and (b) contain motor nerves. The difference (a) can be addressed by choosing the right size of Nerbridge. As for the difference (b), motor nerves will follow a similar regeneration process after the treatment with Nerbridge because peripheral nerves are anatomically, developmentally, and neurophysiologically the same regardless of the regions. Overseas, similar devices are used for any peripheral nerve repair. Publications, etc. show no noteworthy efficacy or safety concern in the regeneration of peripheral nerves, including motor nerves. For these reasons, Nerbridge can be approved for the use in peripheral nerves as with overseas products. However, peripheral nerves in the dura mater should be excluded from the intended use, because the safety of Nerbridge has not been verified for use in the dura mater where the device may come into contact with the cerebrospinal fluid or central nerve.

(3) The instructions for use should include the precautionary statements to the effect that (a) Nerbridge should not be used in patients who are at high risk of wound infection because of severe wound contamination or patients with a severe soft tissue loss, (b) Nerbridge should be carefully implanted for reconstruction of the peripheral nerve adjacent to the joint and appropriate rehabilitation should be performed for patient who underwent such procedure, and (c) Nerbridge should be used by surgeons with sufficient knowledge and experience of nerve reconstruction.

(4) Although the long-term outcome of treatment with Nerbridge was not fully evaluated in the clinical study, most adverse events are likely to occur in the early or middle stage after the treatment. The foreign literature survey, etc. has identified no significant long-term problem. Nevertheless, PMDA instructed the applicant to further investigate long-term outcomes in a post-marketing use-results survey because the publications, etc. indicate that reconstruction of motor nerves may require more time than that of sensory nerves.

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

Intended Use

Nerbridge is intended to be used to bridge a gap between the stumps of the peripheral nerve that has been severed or damaged due to traumatic injury or other causes, thereby inducing regeneration of the nerve and restoring its function (except for the peripheral nerves in the dura mater).

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

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

References

1) U.S. High Production Volume (HPV) Chemical Challenge Program, FINAL SUBMITTAL Tin bis (2-Ethylhexanoate), 201-16735A, December 2007, CAS Number 301-10-0
2) Division of Safety Information, National Institute of Health Sciences. Concise International Chemical Assessment Document. No. 73 Mono- and Disubstituted Methyltin, Butyltin, and Octyltin Compounds (2009)
3) Unno T, Laboratory of Veterinary Pharmacology, Department of Veterinary Science, Faculty of Agriculture, Gifu University. Environmental Toxic Substances—Neurotoxicity of Organotin Compounds, (Special Feature) Wildlife medicine research
4) Konno N, Department of Food Science, Koriyama Women's University & College. Neurotoxicity of organo-tin compounds
5) Robert A, Miller et. Al, *J.Biomed. Mater. Res*. 1977;11:711-719.
6) Rao S, et. Al, *Biomaterials*. 1995;16:1141-1148.
7) John M, et. Al, *J.Biomed.Mater. Res*. 1973;7:155-166.
8) Suenaga N, Minami A, Kato H, et al. Nerve Graft for Digital Nerve Injury: Comparison between posterior interosseous nerve and sural nerve used as a donor nerve (in Japanese). *Journal of Japanese Society of Reconstructive Microsurgery*. 2003;16:21-24.
9) Sunderland S. A classification of peripheral nerve injuries producing loss of function. *Brain*. 1951;74(4):491-516.
10) Kanaya F. Neurorrhaphy (in Japanese). *Journal of Joint Surgery*. 2009;28(3):16-22.
11) Nakao Y. Basic procedures of peripheral nerve operation (in Japanese). *Monthly Book Orthopaedics*. 2009;22(3):17-23.
12) Koshima I. Basics and clinical application of vascularized nerve flap (in Japanese). *Journal of Musculaskeletal System*. 2000;13(8):933-41.
13) Tsuge K. *Principles Practice and of Hand Surgery*. Sixth Edition, Chapter 22, Peripheral nerve injury. Nankodo;1985:349-84.
14) Ibaragi K, Saito H, Yoshitsu T, et al. *Hand Surgery Handbook* (in Japanese), 4 Peripheral nerve injury. Nankodo;2004: 151-63.

15) Green DP, Hotchkiss RN, Pederson WC. *Green's Operative Hand Surgery*. Fourth Edition, Vol. 1. Nerve Injury and Repair. 2003:1510-1621.
16) Millesi H, Meissl G, Berger A. The interfascicular nerve-grafting of the median and ulnar nerves. *The Journal of Bone and Joint Surgery*. 1972;54-A(4):27-50.
17) Donoghoe N, Rosson GD, Dellon AL. Reconstruction of forearm median and ulnar nerve defects with the neurotube. *Microsurgery*. 2007;27:595-600.
18) Rosson GD, William EH, Dellon AL. Motor nerve regeneration across a conduit. *Microsurgery*. 2009;29:107-14.
19) Ashley WW, Weatherly T, Park TS. Collagen nerve guides for surgical repair of brachial plexus birth injury. *Journal of Neurosurgery*. 2006;105:452-56.
20) Kim J, Dellon AL. Reconstruction of a painful post-traumatic medial plantar neuroma with a bioabsorbable nerve conduit: a case report. *Journal of Foot and Ankle Surgery*. 2001;40:318-23.
21) Navissano M, Malan F, Carnino R, Battiston B. Neurotube for facial nerve repair. *Microsurgery*. 2005;25:268-71.
22) Ducic I, Maloney CT, Dellon AL. Reconstruction of the spinal accessory nerve with autograft or neurotube? Two case reports. *Journal of Reconstructive Microsurgery*. 2005;21:29-33.
23) Weber RA, Breidenbach WC, Brown RE, Jabaley ME, Mass DP. A randomized prospective study of polyglycolic acid conduits for digital nerve reconstruction in humans. *Plastic and Reconstructive Surgery*. 2000;106, 5:1036-45.
24) Rinker B, Liau J. A prospective randomized study comparing woven polyglycolic acid and autogenous vein conduits for reconstruction of digital nerve gaps. *Journal of Hand Surgery*. 2011;36A:775-81.
25) Taras JS, Jacoby SM, Lincoski CJ. Reconstruction of digital nerves with collagen conduits. *Journal of Hand Surgery*. 2011;36A:1441-6.
26) Mermans JF et al. Digital nerve injuries: a review of predictors of sensory recovery after microsurgical digital nerve repair. *Hand*. 2012;7:233-41.
27) Merle M, Dellon AL, Campbell JNN, Chang PS. Complications from silicone-polymer intubulation of nerves. *Microsurgery*. 1989;10(2):30-3.