Review Report

February 6, 2009

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following medical device submitted for registration are as follows.

[Category]	Instrument & Apparatus 7　Organ function replacement device
[Generic name]	Coronary stent
[Brand name]	Endeavor Coronary Stent System
[Applicant]	Medtronic Japan Co., Ltd.
[Date of application]	May 9, 2007
[Reviewing office]	Office of Medical Devices

Review Results

February 6, 2009

[Category] Instrument & Apparatus 7 Organ function replacement device

[Generic name] Coronary stent

[Brand name] Endeavor Coronary Stent System

[Applicant] Medtronic Japan Co., Ltd.

[Date of application] May 9, 2007

[Results of review]

The Endeavor Coronary Stent System is a product used for percutaneous coronary stenting, which is comprised of a coronary stent inserted and deployed across the lesion to prop open a coronary artery and a delivery system used to deliver the stent. The surface of the stent is coated with zotarolimus, which is expected to inhibit restenosis.

In a foreign clinical study of the Endeavor Coronary Stent System (ENDEAVOR II), the incidence of the primary endpoint of target vessel failure at 9 months post-procedure was significantly reduced in the Endeavor stent group (7.9%) compared to the control group (a bare metal stent) (15.1%). The secondary efficacy endpoints of target lesion revascularization at 9 months post-procedure, target vessel revascularization at 9 months post-procedure, late loss at 8 months post-procedure, minimal lumen diameter at 8 months post-procedure, and binary restenosis rate at 8 months post-procedure were all significantly in favor of the Endeavor stent and the safety endpoint of the incidence of Major Adverse Cardiac Events at 24 months post-procedure was also significantly reduced in the Endeavor stent group. A clinical study conducted in Japan under similar conditions (ENDEAVOR Japan) produced similar results as the foreign clinical study, demonstrating that there are no racial differences in the efficacy and safety of the Endeavor Coronary Stent System.

A series of non-clinical studies were performed and in addition to the results of physicochemical tests required for metallic stents and delivery systems, as zotarolimus is not approved as a pharmaceutical product in Japan and overseas, the results from pharmacology, toxicology, and pharmacokinetic studies on the zotarolimus drug substance were submitted. In order to assure

the performance of the product as a drug-eluting stent, the results of tests for identification, release rate, and content uniformity etc. of zotarolimus were submitted. Furthermore, the results from pre-clinical studies evaluating efficacy and safety after the implantation of the Endeavor stent in normal coronary arteries of pigs were submitted. Based on overall evaluation of these study results, it has been concluded that the product may be approved.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the intended use as described below, with the following conditions, and that the application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

[Intended use]
Treatment of patients with symptomatic ischemic heart disease due to *de novo* coronary artery lesions with a reference vessel diameter ranging from 2.5 to 3.5 mm and lesion length ≤ 27 mm

[Conditions for approval]
1. Report annually the results of analysis of the prognosis over time for patients included in the clinical studies of the Endeavor Coronary Stent System, i.e. ENDEAVOR I, ENDEAVOR II, ENDEAVOR II-CA, ENDEAVOR III, ENDEAVOR IV, ENDEAVOR Japan, and ENDEAVOR US PK and take appropriate action as needed.
2. Report the results of analysis of the long-term prognosis over time based on the data from use-results surveys and take appropriate action as needed.
3. Promptly report the cases of stent thrombosis associated with the use of the Endeavor stents occurring in Japan during the re-examination period and take appropriate action as needed.

Review Report

February 6, 2009

I. Product for Review

[Category]	Instrument & Apparatus 7　Organ function replacement device
[Generic name]	Coronary stent
[Brand name]	Endeavor Coronary Stent System
[Applicant]	Medtronic Japan Co., Ltd.
[Date of application]	May 9, 2007
[Proposed intended use]	Treatment of patients with symptomatic ischemic heart disease due to *de novo* coronary artery lesions with a reference vessel diameter ranging from 2.25 to 3.5 mm and lesion length ≤ 27 mm

II. Product Overview

The Endeavor Coronary Stent System is a product used for percutaneous coronary stenting, which is comprised of a stent inserted and deployed across the lesion to prop open a coronary artery and a delivery catheter used to deliver the stent to the lesion site. The stent is coated with zotarolimus in order to locally inhibit neointimal proliferation, which is considered to be the cause of in-stent restenosis.

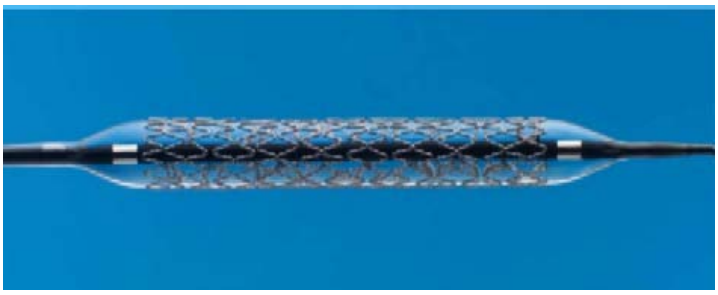

Figure 1　Appearance of the Endeavor stent

The stent platforms for the Endeavor stents with different diameters are the stent components of the Driver Coronary Stent System (stent diameter, 3.0-3.5 mm; Approval number, 21600BZY00298000) and the Micro-Driver Coronary Stent System (stent diameter, 2.5-2.75 mm; Approval number, 21800BZY10179000), which are made of cobalt-chromium-nickel-molybdenum alloy (MP35N), and the metal surface of the Endeavor stent is coated with a mixture of zotarolimus (Figure 2), which is structurally-related to

sirolimus, an immunosuppressant and phosphorylcholine (PC) polymer. The Endeavor stent delivery system uses the same materials as the delivery system utilized for the aforementioned Driver (and Micro-Driver) Coronary Stent System, except for the materials of the balloon, and the balloon uses the same materials as [redacted] (Approval number, [redacted]).

Sirolimus has been used on the Cypher stent (Approval number, 21600BZY00136000, Johnson & Johnson K.K.) and paclitaxel on the TAXUS Express2 stent (Approval number, 21900BZX00340000, Boston Scientific Japan K.K.) as drug coating for drug-eluting stents (DES), but the Endeavor stent represents the first use of zotarolimus in Japan.

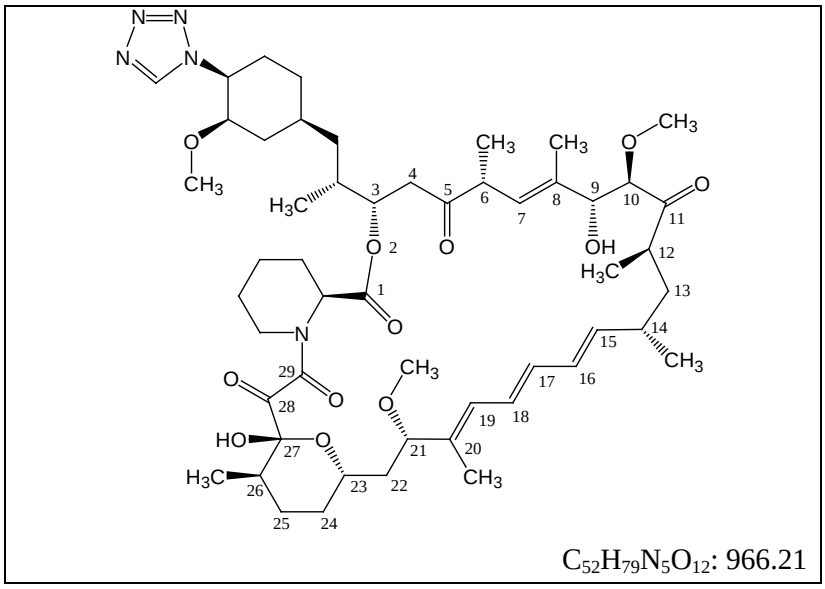

Figure 2 Chemical structure of zotarolimus

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

With regard to this application, the data submitted by the applicant and the applicant's responses to the questions from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

[Origin or history of discovery]

Coronary stenting, which emerged as an endovascular therapy for ischemic heart disease, has reduced complications of acute coronary artery occlusion and restenosis etc. and is now

widespread to the extent that metallic stents are placed in more than 80% of cases of coronary intervention. On the other hand, it has been revealed that the placement of a metallic stent in a blood vessel causes an inflammatory response induced by vascular wall injuries or via foreign body reaction etc., which induces/promotes neointimal formation in the subsequent healing process of the vessel wall, leading to vascular restenosis on a long-term basis in not a few cases. This has been considered as the biggest problem with stent therapy.

In recent years, many publications reported that sirolimus, a cell-cycle inhibitor, reduces neointimal hyperplasia and associated restenosis rates. Then, Abbott Laboratories (the US) took notice of zotarolimus in the development of a novel drug with a similar mechanism of action to sirolimus. Although zotarolimus was originally developed as an immunosuppressant, as it was difficult to formulate it for systemic administration, its development as a pharmaceutical product was given up. Meanwhile, as zotarolimus had been identified as a potent smooth muscle cell growth inhibitor, Medtronic Vascular (the US) decided to have zotarolimus supplied from Abbott Laboratories through a licensing agreement and develop it as a drug coated on DES to inhibit neointimal proliferation. As the polymer coating on the stent (a carrier for the drug) is required to meet some requirements, e.g. affinity for the stent platform and biocompatibility with the vessel wall, the PC polymer was employed, which has been used on coronary stent in the US ([redacted], approved [redacted] 20[redacted]). Based on the results of dose-finding studies etc. in a porcine coronary artery model, the Endeavor stent coated with 10 μg/mm zotarolimus was developed.

[Usage conditions in foreign countries]

In European countries, in July 2005, the Endeavor Coronary Stent System received CE mark approval for improving coronary luminal diameter and reducing restenosis in patients with symptomatic ischemic heart disease in *de novo* coronary artery lesions in native coronary arteries with a reference vessel diameter of 2.25 mm to 4.0 mm and a lesion length of ≤ 27 mm and has been marketed. In the US, the product received FDA approval in February 2008 for improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* lesions of length≤ 27 mm in native coronary arteries with reference vessel diameters of≥ 2.5 mm to ≤ 3.5 mm and has been marketed.

As of December 2008, the product is used in more than 100 countries worldwide and approximately [redacted] systems have been distributed.

[Occurrence of malfunctions associated with the use of the Endeavor Coronary Stent System or similar medical devices]

As of December 2008, the incidence of malfunctions was 0.22% (reports/ patients) and regarding device-related deaths and serious malfunctions or deaths and serious malfunctions for which a causal relationship to the device can not be excluded, the incidence of deaths was 0.0161% (cases) and the incidence of stent thrombosis was 0.0170% (cases). The 5 most frequently reported malfunctions associated with the use of the Endeavor Coronary Stent System were the same as those associated with the use of its bare-metal platform stent, i.e. the Driver Coronary Stent System, which were stent dislodgement during the procedure (0.04%), stent deformation (before stent placement, 0.01%; after stent placement, 0.03%), stent migration (0.03%), and difficulty in stent positioning (0.02%), and all of them were related to the stent, not the drug.

On the other hand, there were 4 drug-related malfunctions accompanied by a physiological response (2 reports of pyrexia, 2 reports of severe rash), according to a review of all post-marketing malfunctions reported since the product's introduction into the market. However, these were considered to be adverse events associated with antiplatelet medications and contrast agent used concomitantly with the Endeavor Coronary Stent System and none of them were considered to be caused by zotarolimus.[1)]

2. Setting of specifications

The performance and physical specifications for the Endeavor zotarolimus-coated stent and stent delivery system were set based on the US FDA guidance "Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: Intravascular Stents, Jan 2005" and "Handling of Approval Applications for Coronary Stents" (PFSB/ELD Notification No. 0904001 dated September 4, 2003) and the all submitted test results met the specifications. Since stent material characterization, dimension, extractable substances, and percent surface area after expansion, chemical composition and mechanical properties of the cobalt-based alloy, evaluation of the galvanic effects, stent cell area after expansion, and stent dimension after expansion are the same as the approved bare-metal platform stent, no test results were submitted.

Concerning drug elution, the specifications are set for the status of the PC polymer in the drug coating layer on the stent, drug content, identification of zotarolimus, drug content uniformity, residual solvents, content, total related substances and individual related substances, zotarolimus elution rate, and insoluble particulate matters, and the

submitted test results met the specifications for each attribute.

PMDA reviewed and accepted the above specification data.

3. Stability and durability

The long-term storage stability of the drug coating was evaluated on real-time samples stored for [redacted] years in accordance with the ICH guidelines. In addition to the specification tests, photostability testing and temperature cycle test were performed as stress tests and the submitted test results showed no problems. On the other hand, the Endeavor stent delivery system was tested for the stent maximum gap, in addition to the test attributes included in the product specifications, using real-time samples (up to [redacted] years and [redacted] years) and accelerated aged samples (equivalent to [redacted] years and [redacted] years), and the submitted test results showed no problems.

PMDA reviewed the stability and durability data on the product and determined that the expiration period of 2 years proposed by the applicant is acceptable.

4. Conformity to the requirements specified in Paragraph 3 of Article 41 of the Pharmaceutical Affairs Law

A declaration of conformity declaring that the product meets the requirements 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 Law (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Notification No. 122, 2005) and the Ministerial Ordinance on Quality Management System for Medical Devices and *In Vitro* Diagnostics (MHLW Ministerial Ordinance No. 169, 2004) was submitted.

PMDA reviewed the product's conformity to the Essential Principles and accepted the declaration.

5. Performance

[Studies to support safety]

The biological safety of the balloon of the delivery system and the PC polymer-coated stent, which are different from those of the approved bare-metal stent system, was evaluated. The balloon was tested for cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, pyrogenicity, and hemolysis in accordance with ISO10993 and all tests produced

negative results and these test results were submitted. On the other hand, the PC polymer-coated stent was tested for cytotoxicity, sensitization, acute systemic toxicity, subacute toxicity, bacterial reverse mutation, chromosomal aberration in mammalian cells, local effects after implantation, hemolysis, partial thromboplastin time, and hemocompatibility, and all tests except for the implantation test produced negative results and these test results were submitted.

In the 4-week subcutaneous implantation test, microscopically, the test material (the PC polymer-coated stent) produced mild inflammation compared to the control material (the Driver stent) and moderate inflammation compared to the negative control material (USP polyethylene reference strips). Thus, a chronic toxicity study on long-term (13 weeks) subcutaneous implantation was conducted. As a result, there were no signs of systemic toxicity associated with the test material and the test material was macroscopically and microscopically non-inflammatory at the site of implantation as well.

The following toxicity studies on zotarolimus were conducted in accordance with drug development guidelines: single intravenous dose toxicity studies (rats, monkeys), 28-day and 90-day repeated dose toxicity studies (rats, monkeys), a testicular toxicity study (rats), genotoxicity studies (reverse mutation assay, chromosomal aberration assay, mouse micronucleus assay), reproductive and developmental toxicity studies (rats, rabbits), an antigenicity study in guinea pigs, and murine local lymph node assay. Zotarolimus was administered at doses of up to 75 μg/kg/day in the single intravenous dose toxicity studies (rats, monkeys) and at doses of up to 100 μg/kg/day in the 28-day, repeated dose toxicity study (rats) and no clear toxicity was observed. The 28-day and 90-day repeated dose toxicity studies (monkeys) showed no clear toxicity at doses of up to 100 μg/kg/day. The genotoxicity studies all produced negative results. The reproductive and developmental toxicity studies evaluated effects on embryo-fetal development in rats or rabbits and effects on reproduction and fertility in rats (males, females). As a result, the no observed adverse effect levels (NOAELs) for embryo-fetal development were 100 μg/kg/day in rabbits and 25 μg/kg/day in rats, the NOAELs for maternal general toxicity with respect to embryo-fetal development were 30 μg/kg/day in rabbits and 60 μg/kg/day in rats, the NOAEL for reproduction and fertility in male rats was 10 μg/kg/day, the NOAEL for general toxicity in female rats was 30 μg/kg/day, and the NOAEL for fertility and embryonic development in female rats was 100 μg/kg/day. The NOAEL in the rat testicular toxicity study was 10 μg/kg/day and the results of the antigenicity and skin sensitization studies were negative.

PMDA reviewed the safety data, taking account of comments from the Expert Discussion. As a

result, PMDA judged that these inflammatory findings will not become a major problem in clinical use, because the inflammatory reactions noted in the implantation test may have been caused by physical irritation, and the histopathological evaluation etc. in other implantation tests conducted under conditions closer to clinical use (implantation into porcine coronary arteries, described later) than the subcutaneous implantation tests, revealed that the inflammatory findings were not strong. On the other hand, concerning the toxicity of zotarolimus, PMDA judged that clinically relevant toxicity is unlikely to occur since there were no significant toxic findings over the dose range estimated from the amount of the drug coated on the stent (10 μg/mm), the blood concentrations of the drug released from the stent (the maximum blood concentration in humans is around 3 ng/mL after the implantation of a 30 mm length stent), and the pharmacokinetics.

Zotarolimus is an unapproved drug and there is a concern that adequate information on zotarolimus will not be available in clinical practice. Therefore, it is recommended that adequate information on zotarolimus in addition to the product information should be provided to the product users in clinical practice in order to ensure the safe use of the product.

[Tests to support performance]

In order to support the performance of the Endeavor stent, the tests as listed in the document on the setting of specifications were performed and the test results, which met the specifications for each attribute, were submitted. Packaging and labeling tests including visual inspection of packages, package seal strength testing, and tests for oxygen percentage in the package, were performed and the submitted test results showed no problems.

PMDA reviewed and accepted the data on tests to support performance.

[Studies to support efficacy]

In order to support the efficacy of the product, zotarolimus general pharmacology, mechanism, and immunosuppression studies were conducted. As general pharmacology data, the results from various (different receptors) receptor-ligand binding assays and studies to determine the effects on the central nervous, respiratory, and cardiovascular systems were submitted and these studies showed no particular problems except for zotarolimus exhibiting affinity for some receptors in the receptor-ligand binding assays.

As zotarolimus binds to FKBP-12, leading to the formation of a complex with mTOR, inhibiting its activity, the mechanism studies investigated FKBP-12 affinity, the effect on the proliferation

of human coronary artery smooth muscle and endothelial cells, and the effect of [redacted] ([redacted] [hereinafter referred to as "[redacted]"]) on the inhibition of human coronary artery smooth muscle cell proliferation. The binding affinity of zotarolimus with FKBP-12 was measured by inhibitory activity against the binding of tacrolimus to FKBP-12. As a result, the IC_{50} values of zotarolimus and sirolimus were 2.8 ± 0.4 nM and 1.7 ± 0.2 nM, respectively, suggesting that these compounds have similar binding affinity. Zotarolimus inhibited the proliferation of human coronary artery smooth muscle and endothelial cells in a concentration-dependent manner and the IC_{50} values were 2.9 ± 0.7 nM (smooth muscle cells) and 2.6 ± 1.0 nM (endothelial cells). Zotarolimus was demonstrated to have almost comparable inhibitory activity as compared to the inhibitory concentrations of sirolimus against cell proliferation (IC_{50} = 0.8 ± 0.6 nM [smooth muscle cells] and 2.0 ± 1.3 nM [endothelial cells]). Inhibition of human coronary artery smooth muscle cell proliferation by zotarolimus was unaffected by the presence of [redacted], suggesting that the efficacy is unaffected even when [redacted] remains in zotarolimus as [redacted]. The above results indicated that like sirolimus, zotarolimus inhibits cell proliferation by affecting the cell cycle via binding to FKBP-12.

In order to investigate the immunosuppressive effects that its analogs such as sirolimus have, concanavalin A-induced T-cell proliferation, the effect on mixed lymphocyte reaction, the effect of phosphorylcholine on the inhibition of IL-2 secretion in human CD4+ T-helper cells, and the effect on platelets were studied, which indicated that zotarolimus has immunosuppressive effects like sirolimus. These results suggested that zotarolimus structurally related to sirolimus has similar pharmacological effects as sirolimus and can contribute to the inhibition of neointimal proliferation by inhibiting human coronary artery smooth muscle cell proliferation through almost the same route as sirolimus.

PMDA asked the applicant to explain the following points on the pharmacological effects of zotarolimus.

1. According to the ligand-receptor binding assays, zotarolimus exhibited affinity for some receptors. Thus, examine the risks of unexpected adverse effects etc. associated with the use of the product.
2. As the inhibitory concentrations of zotarolimus against proliferation of vascular smooth muscle cells and endothelial cells are almost identical, the possibility that zotarolimus inhibits the proliferation of vascular endothelial cells while inhibiting the proliferation of vascular smooth muscle cells is inferred. Discuss the potential risks in clinical use, e.g. a delay in endothelialization due to inhibition of proliferation of vascular endothelial cells.

The applicant responded as follows:

1. In the ligand-receptor binding assays, the inhibitory activity of high concentrations of zotarolimus against binding of each ligand to its receptor was measured. It is estimated from the results of pharmacokinetic studies that maximum blood concentrations of zotarolimus and free drug concentrations following stent implantation are very low and zotarolimus is very unlikely to interact with these receptors at around C_{max}. Therefore, the possibility of clinical risks should be low.

2. As physical injury to endothelial cells occurs due to stent expansion, the cells that are in direct contact with the stent are believed to be vascular smooth muscle cells. Thus, it is considered that the drug eluted early after stent expansion is promptly taken up by adjacent smooth muscle tissue and then regeneration of vascular endothelial cells starts. The inhibitory concentrations for vascular smooth muscle cells and endothelial cells are close and the possibility that the drug acts on endothelial cells in arterial tissue can not be ruled out. However, considering the time course as mentioned above, the drug coated on the stent comes in contact with vascular smooth muscle cells at the time of stent expansion when its peak elution occurs and it is inferred that the effect on regenerated endothelial cells is insignificant. Indeed, a 28-day safety study in pigs demonstrated complete luminal coverage with endothelial cells, with no significant difference compared to a bare-metal stent. Therefore, there should be no major problem concerning a delay in endothelialization.

PMDA determined that the applicant's view (Based on the results of pharmacokinetic studies, a blood concentration range where zotarolimus exhibits non-specific receptor binding activity is unlikely to be maintained and stent implantation does not yield unintended pharmacological effects or systemic effects including immunosuppression) is largely acceptable. As to the action of zotarolimus on vascular smooth muscle and endothelial cells, as sufficient evidence to prove the hypothesis has not been presented, e.g. tissue drug concentrations at different timepoints have not been measured, the kinetics of the drug in tissue is unknown. Meanwhile, there was no delay in endothelialization in stented porcine coronary arteries and the assessment of endothelial function (reference data, described later) showed that endothelial function was normal. Therefore, taking account of comments from the Expert Discussion, PMDA accepted the applicant's view that the possibility of the occurrence of unintended adverse events associated with zotarolimus is low.

[Pharmacokinetics]

Regarding the pharmacokinetics of zotarolimus after implantation of the Endeavor stent, the results of the following studies were submitted: assay to measure the *in vitro* release kinetics of the drug and *in vivo* elution study (after stent implantation in swine coronary arteries or rabbit illiac arteries, the stents were removed at various timepoints to determine the amount of the drug remaining on the stent). In the *in vivo* study, the following parameters were also measured and the results were submitted: blood drug concentrations, drug levels in tissues at the site of stent implantation (proximal and distal sites), and drug levels in lung, liver, and kidney tissues and myocardium immediately beneath the stents that were taken and prepared at the time of stent removal. Human pharmacokinetic and safety data from a phase I escalating, single intravenous-dose study (60 subjects) and a phase I multiple dose (14 days), intravenous study (72 subjects) of zotarolimus were also submitted.

For the measurement of blood drug levels in the swine and rabbit, stents coated with 120 μg zotarolimus (stent length, 12 mm) were implanted. In the swine, blood levels were 2.67 ± 0.67 ng/mL at 3 hours after implantation. In the rabbit, blood levels peaked at 15 minutes (177.68 ± 167.07 ng/mL) and then declined to 1.88 ± 0.31 ng/mL at 24 hours after implantation. The highest concentration of zotarolimus was observed in the vessel wall surrounding the stent at 2 days after implantation in the swine (27.85 ± 9.59 ng/mg) and rabbit (69.07 ± 30.68 ng/mg) and this level declined to about 1 ng/mg at 28 days after implantation in both models.

In the phase I clinical studies in humans, the zotarolimus concentration was 110.78 ng/mL at 5 minutes after intravenous administration of 900 μg and the zotarolimus concentration following intravenous administration of 300 μg, which corresponds to the amount of the drug coated on a 30 mm length stent, was 36.71 ng/mL. The half-life ($t_{1/2}$) following the administration of 300 μg was 35.9 ± 4.6 hours, which was shorter than the half-life of sirolimus, i.e. approximately 60 hours (single oral dose administration). No clinical or biochemical evidence of systemic immunosuppression or toxicities were found at up to 900 μg.

PMDA decided to evaluate the pharmacokinetics of zotarolimus after implantation of the Endeavor stent together with the results from human pharmacokinetic studies (ENDEAVOR US PK, ENDEAVOR Japan PK) (described later).

[Studies to support usage method]

In order to support the usage of the Endeavor Coronary Stent System, dose-finding studies in a normal porcine coronary artery model, a subacute performance study, histopathological

evaluation after stent implantation, and evaluation of overexpanded stents and stent implantation into small vessels were performed and these study results were submitted. The results of assessment of endothelial function in porcine coronary arteries were also submitted as reference data.

In the dose-finding studies in a normal porcine coronary artery model (single stents coated with zotarolimus at a dose of [redacted], [redacted], 10, and [redacted] μg/mm stent length or overlapped stents coated with zotarolimus at a dose of 10 and [redacted] μg/mm were used, polymer-only coated stents and Driver stents were used as the controls), the device's acute performance, angiography, histomorphometry, and histopathology were evaluated at [redacted] days, [redacted] days, and [redacted] days after implantation. No drug-related effects or local tissue toxicities were noted at the site of implantation of the drug-eluting stents with different doses or overlapped stents. In [redacted]-day implantation test, restenosis was inhibited at the doses of 10 μg/mm and [redacted] μg/mm, but there were no differences in the inhibitory effect between the doses. Thus, in consideration of safety, a dose of 10 μg/mm was chosen for the product. There were no significant differences in the intima and healing response at [redacted] days between the drug-coated stents and the Driver stents. Although no significant differences were observed for intimal thickness and percent stenosis between the drug-coated stents and the Driver stents, there was a trend towards improvement in the Endeavor 10 μg/mm group compared to the control groups. Concerning inflammatory response, the polymer-coated stents and the stents coated with 10 μg/mm of zotarolimus had significantly higher inflammation scores, but the inflammatory response was not strong. The overlapped Endeavor stents exhibited higher inflammation scores, higher histology injury scores, and greater medial thinning than the overlapped Driver stents, but these differences were minor and there was no response that would become a clinically significant problem.

In the subacute performance study, in addition to the evaluation of the device's acute performance, angiography, histomorphometry, and histopathology at [redacted] days after implantation, quantitative assessment of neointimal cell proliferation by immunohistochemistry and examination of subacute thrombogenicity based on thrombus deposition were performed. In both the Endeavor [redacted] μg/mm and 10 μg/mm groups, neointimal cell proliferation was inhibited by about 50%. There were no differences in subacute thrombogenicity between the Endeavor and control groups. In the endothelial function assessment study in porcine coronary arteries, after the Endeavor stents were implanted in porcine coronary arteries, endothelial nitric oxide synthase (eNOS) mRNA and eNOS protein expression at the site of stent implantation were analyzed and endothelial function following acetylcholine challenge was assessed. As a result, there were no particular problems.

In [redacted]- to [redacted]-day implantation tests in a normal porcine coronary artery model, the safety at the site of stent implantation was evaluated. As a result, since polymer-like fragments were found in the area around the stent struts, the vessels implanted with the stents and myocardium tissue were reevaluated using high-power microscopy. All of the polymer-like fragments were fully encapsulated in the neointima and none of them were seen protruding into the arterial lumens. Therefore, polymer-like fragments, if any, are localized and the risk of embolism should be low.

Using an overexpansion model where the Endeavor 10 μg/mm stents and Driver stents were overdilated to [redacted]% and [redacted]% normal vessel diameter, the device's acute performance, angiography, histomorphometry, and histopathology were evaluated at [redacted] days after implantation. The Endeavor 10 μg/mm stents overexpanded to [redacted]% and [redacted]% normal diameter had higher fibrin and inflammation scores, but these differences were not large and there was no response that would become a clinically significant problem.

Stent implantation into small vessels was evaluated by the device's acute performance, angiography, histomorphometry, and histopathology at [redacted] days after implantation, using the 2.25 mm and 2.5 mm diameter Endeavor stents or Micro-Driver stents. Except for the above-mentioned level of increased inflammation scores etc. observed in the Endeavor stent group, there were no problematic findings.

PMDA reviewed the inflammatory findings following the implantation of the Endeavor stent, including significantly higher inflammation scores etc. observed in some animal model studies and polymer-like fragments around the stent struts. As a result, taking account of comments from the Expert Discussion, PMDA accepted the applicant's view that these inflammatory responses are unlikely to become a clinically significant problem.

6. Risk analysis

Documents summarizing the risk management system and its implementation status in reference to ISO 14971 "Medical devices - Application of risk management to medical devices" were attached. Documents summarizing the results of analysis of hazards against which safety measures were requested by the MHLW etc. with respect to bare metal stents and drug-eluting stents, and the risk reduction measures taken, were also submitted.

PMDA reviewed and accepted the risk analysis data.

7. Manufacturing process

Data on Sterility Assurance Level, sterilization parameters and residual ethylene oxide were submitted as sterilization method information.

PMDA reviewed and accepted the data on manufacturing process.

8. Clinical data

Clinical study data from a foreign ENDEAVOR II study and a domestic ENDEAVOR Japan study were submitted. In addition, the results from the ENDEAVOR I study (a pilot study), the ENDEAVOR III study (a comparative study vs. the Cypher stent), and the ENDEAVOR IV study (a comparative study vs. the TAXUS Express2 stent) were submitted as reference data.

[ENDEAVOR II, ENDEAVOR Japan]

A prospective, multi-center, double-blind, two-arm randomized controlled study was conducted at 72 sites in Europe etc. to evaluate the efficacy and safety of the Endeavor stent (598 patients) compared to the Driver control stent (599 patients) in patients with single *de novo* lesions of native coronary arteries with reference vessel diameters $\geq$ 2.25 mm and $\leq$ 3.5 mm and lesion lengths of $\geq$ 14 mm and $\leq$ 27 mm (ENDEAVOR II). The primary endpoint was the target vessel failure (TVF) rate at 9 months post-procedure and the secondary endpoints were target lesion revascularization (TLR) at 9 months post-procedure, target vessel revascularization (TVR) at 9 months post-procedure, device success, lesion success, procedure success, major adverse cardiac event (MACE) rates at 30 days and 6, 9, 12, and 24 months post-procedure, late loss at 8 months post-procedure, in-stent and in-segment minimal lumen diameters at 8 months post-procedure, in-stent and in-segment binary restenosis rates at 8 months post-procedure, and neointimal hyperplastic volume at 8 months post-procedure as measured by intravascular ultrasound (IVUS). Following the procedure, patients received antiplatelet therapy with aspirin indefinitely and clopidogrel sulfate for 12 weeks, as a general rule. Follow-up through [redacted] years in this study has been planned and the results of follow-up through [redacted] years have been submitted as reference data.

A prospective, multi-center, single-arm, non-randomized study (11 sites, 99 patients) in the same patient population as the ENDEAVOR II study was conducted to confirm the efficacy and safety of the Endeavor stent in Japanese patients (ENDEAVOR Japan). The same endpoints as the ENDEAVOR II study were chosen except that neointimal hyperplastic volume by IVUS (a secondary endpoint) was not evaluated and MACE rate was followed up to 9 months. Following the procedure, patients received antiplatelet therapy with aspirin indefinitely and

ticlopidine hydrochloride for a minimum of 12 weeks, as a general rule.

The results of the ENDEAVOR II and ENDEAVOR Japan studies are presented in Table 1. In the ENDEAVOR II study, the primary endpoint of TVF rate at 9 months post-procedure was 7.9% in the Endeavor stent group, which was significantly lower than 15.1% in the control group ($P < 0.001$, between-group comparison by Wilcoxon and log-rank tests), demonstrating the superiority of the Endeavor stent over a bare metal stent. TLR and TVR rates at 9 months post-procedure and MACE rates at 9, 12, and 24 months post-procedure were significantly reduced in the Endeavor stent group compared to the control group.

In the ENDEAVOR Japan study, the primary endpoint of TVF rate at 9 months post-procedure was 5.2%, which was not inferior to that in the pivotal study, i.e. the ENDEAVOR II study. The results of this study were compared to those of the ENDEAVOR II study, adjusted for propensity scores based on the patient background. As a result, there were no significant differences compared to the ENDEAVOR II results and it has been determined that the ENDEAVOR II study can be extrapolated into the Japanese population as well.

Table 1 ENDEAVOR II and ENDEAVOR Japan results

	ENDEAVOR II			ENDEAVOR Japan
Endpoint	Endeavor (n = 598)	Control (n = 599)	*P*-value	Endeavor (n = 99)
TVF at 9 months post-procedure (%)	7.9	15.1	< 0.001	5.2
TLR at 9 months post-procedure (%)	4.6	11.8	< 0.001	3.1
TVR at 9 months post-procedure (%)	5.6	12.5	< 0.001	3.1
Device success (%)	98.8	99.2	0.773	97.0
Lesion success (%)	99.7	100	0.249	100
Procedure success (%)	97.3	97.1	1.000	98.0
MACE (%) (to 30 days)	2.9	3.7	0.421	2.0
(to 6 months)	4.6	8.9	0.004	2.0
(to 9 months)	7.3	14.4	< 0.001	5.2
(to 12 months)	8.8	15.6	< 0.001	--
(to 24 months)	9.9	18.3	< 0.001	--
Eight-month late loss (mm)	0.62 ± 0.46	1.03 ± 0.59	< 0.001	0.53 ± 0.43
(in-stent/in-segment)	0.36 ± 0.46	0.72 ± 0.61	< 0.001	0.23 ± 0.42
Eight-month minimal lumen diameter (mm)	1.99 ± 0.56	1.62 ± 0.70	< 0.001	2.15 ± 0.63
(in-stent/in-segment)	1.86 ± 0.55	1.56 ± 0.67	< 0.001	2.00 ± 0.57
Eight-month binary restenosis (%)	9.5	33.2	< 0.001	8.2
(in-stent/in-segment)	13.3	34.7	< 0.001	8.2
Neointimal hyperplasia volume (mm^3)	30.15	53.51	< 0.001	--

Table 2 Incidence of principal adverse events in ENDEAVOR II and ENDEAVOR Japan (%)

	ENDEAVOR II (to 720 days post-procedure)			ENDEAVOR Japan (to 270 days post-procedure)
Description of adverse event	Endeavor (n = 583)	Control (n = 579)	*P*-value	Endeavor (n = 97)
MACE	9.9 (58/583)	18.3 (106/579)	< 0.001	5.2 (5/97)
Death	2.1 (12/583)	2.2 (13/579)	0.843	0.0 (0/97)
Q wave myocardial infarction	0.3 (2/583)	0.9 (5/579)	0.286	0.0 (0/97)
Non-Q wave myocardial infarction	2.6 (15/583)	3.1 (18/579)	0.601	2.1 (2/97)
Emergent CABG	0.0 (0/583)	0.0 (0/579)	--	0.0 (0/97)
Perforation	0.5 (3/583)	0.3 (2/579)	1.000	0.0 (0/97)
Acute stent thrombosis	0.5 (3/583)	1.2 (7/579)	0.223	0.0 (0/97)
Late stent thrombosis	0.0 (0/583)	0.0 (0/579)	--	0.0 (0/97)
Vascular complications	0.5 (3/583)	1.2 (7/579)	0.223	0.0 (0/97)
Cerebrovascular accident	0.7 (4/583)	0.5 (3/579)	1.000	0.0 (0/97)
Major bleeding complications	1.2 (7/583)	2.2 (13/579)	0.184	0.0 (0/97)

Principal adverse events to 720 days post-procedure in the Endeavor and control groups are shown in Table 2. In the ENDEAVOR II study, 12 deaths occurred in the Endeavor group (2.1%, 12 of 583 patients), which include 8 cardiac deaths and 4 non-cardiac deaths. In the ENDEAVOR Japan study, there were no deaths and 5 patients experienced MACE up to 270 days post-procedure.

PMDA checked on the diameters of the stents used in the clinical studies submitted as evaluation data. As a result, the number of cases of the use of 2.25 mm diameter stents, which are unapproved for elective use in Japan (16 stents in the ENDEAVOR II study, 4 stents in the ENDEAVOR Japan study), was limited and considering that these studies did not provide adequate assurance of the efficacy and safety of the Endeavor 2.25 mm stents in smaller vessels, PMDA asked the applicant to provide a justification for the claim that the efficacy and safety of 2.25 mm stents can be confirmed in these clinical studies. The applicant responded that the 2.25 mm diameter stent would be removed from the application for approval.

Since the superiority of the Endeavor stent over the control stent in the primary endpoint has been demonstrated and there were no particular problems with the secondary efficacy and safety endpoints as well, taking account of comments from the Expert Discussion, PMDA accepted the applicant's view that the efficacy and safety of the Endeavor Coronary Stent System have been confirmed and their removal of the 2.25 mm diameter stent from the application.

[Pharmacokinetic studies (ENDEAVOR Japan PK, ENDEAVOR US PK)]

A zotarolimus pharmacokinetic study was conducted in 43 patients in the US to measure blood drug concentrations after the implantation of the Endeavor stents (ENDEAVOR US PK). A 20 patient pharmacokinetic study was also conducted as part of the ENDEAVOR Japan study to measure blood drug concentrations in Japanese patients and assess the ability to extrapolate foreign clinical data to Japan (ENDEAVOR Japan PK).

In the US zotarolimus pharmacokinetic study, zotarolimus concentrations in venous blood were measured repeatedly up to 720 hours after the implantation of stents coated with doses including 180, 240, and 300 μg zotarolimus. The results of pharmacokinetic analysis using a non-compartmental model are presented in Table 3. The maximum blood concentration (2.66 ± 1.00 ng/mL) after the implantation of stents coated with 300 μg was comparable to or slightly lower than the trough concentrations of its analog as an immunosuppressant (approximately 3-8 ng/mL) and was also comparable as compared to that of a currently available DES, i.e. the Cypher stent (two 18-mm-length stents, 2 ng/mL). In the Japanese pharmacokinetic study, blood was collected at the same sampling times as in the ENDEAVOR US PK study after the implantation of stents coated with zotarolimus at doses of 180 to 380 μg and pharmacokinetic analysis was performed in the same manner. As a result, there were no major differences between the Japanese and US studies (Table 3). The maximum blood concentration in a Japanese subject implanted with stent coated with the highest dose of 380 μg was 5.64 ng/mL.

Table 3 Results of pharmacokinetic studies (ENDEAVOR Japan PK, ENDEAVOR US PK)

Pharmacokinetic parameter	180 μg dose group (N = 7 / 24)	240 μg dose group (N = 8 / 6)	300 μg dose group (N = 2 / 7)	380 μg dose group (N = 1)
C_{max} (ng/mL)	1.80 ± 0.53	3.14 ± 0.48	3.19	5.64
	1.51 ± 0.62	1.83 ± 0.21	2.66 ± 1.00	—
T_{max} (h)	1.3 ± 0.5	1.6 ± 0.5	1.3	1.9
	1.2 ± 0.6	1.4 ± 1.3	1.5 ± 1.3	—
$AUC_{0\text{-}24}$ (ng·h/mL)	21.73 ± 7.77	39.44 ± 6.08	38.86	83.97
	20.02 ± 6.45	23.68 ± 3.57	31.45 ± 9.17	—
$AUC_{0\text{-}last}$ (ng·h/mL)	60.92 ± 19.73	90.47 ± 6.96	111.55	201.53
	57.02 ± 13.46	63.83 ± 15.27	90.77 ± 19.51	—
$AUC_{0\text{-}inf}$ (ng·h/mL)	69.35 ± 19.20	100.06 ± 7.23	127.91	233.39
	66.61 ± 14.86	72.84 ± 19.96	101.45 ± 23.48	—
β (l/h)	0.012 ± 0.002	0.013 ± 0.002	0.008	0.010
	0.012 ± 0.003	0.012 ± 0.002	0.012 ± 0.003	—
$t_{1/2}$ (h)	59.8 ± 11.2	54.0 ± 7.8	91.9	66.5
	59.7 ± 14.4	57.5 ± 7.6	59.5 ± 16.1	—
Vd_{β}/F (L)	251.0 ± 95.2	191.4 ± 32.4	329.2	156.2
	254.7 ± 74.5	288.5 ± 53.6	291.6 ± 113.7	—
CL/F (L/h)	2.7 ± 0.6	2.4 ± 0.2	2.4	1.6
	2.8 ± 0.7	3.5 ± 1.0	3.1 ± 0.8	—

Pharmacokinetic parameters of the Endeavor stent (upper row, ENDEAVOR Japan PK; lower row, ENDEAVOR US PK; no SD was reported when N = 1 or 2)

PMDA asked the applicant to discuss the onset of systemic pharmacological effects associated with the use of the Endeavor Coronary Stent System, taking into account that trough concentrations of zotarolimus in humans have not been determined.

The applicant responded as follows:

The IC_{50} value for the inhibition of human IL-2-dependent T cell proliferation was 1.2 nM for zotarolimus and 0.95 nM for sirolimus and the IC_{50} value for the inhibition of concanavalin A-induced cell proliferation was 7.0 nM for zotarolimus and 2.4 nM for sirolimus, indicating that zotarolimus and sirolimus have almost comparable immunosuppressive potential. It is also inferred from the results of zotarolimus repeated-dose toxicity studies that the dose range at which an immunosuppressive effect occurs is not substantially different between zotarolimus

and sirolimus. As an immunosuppressant, sirolimus is usually administered at a dose of about 2 mg/day. On the other hand, although the maximum blood concentration after the implantation of 30 mm length Endeavor stents (corresponding to 300 μg zotarolimus) was almost comparable to the trough concentrations of the immunosuppressant, zotarolimus is not administered continuously and elevations of blood concentrations are transient and in a human phase I study, no systemic immunotoxic effects were observed following a single intravenous administration of zotarolimus 900 μg though the route of administration was different. In light of these findings, the possibility of the onset of systemic immunosuppressive effects associated with the use of the Endeavor Coronary Stent System should be very low.

According to the applicant's view, while the estimated trough concentrations of zotarolimus to have immunosuppressive effects based on its pharmacological effects etc. are close to the maximum blood concentration of zotarolimus following the implantation of the Endeavor stents and there is a concern about the onset of systemic immunosuppressive effects, maintenance of blood levels is required for the onset of immunosuppressive effects and even when all of the total amount of the drug loaded on the stent is released into the systemic circulation, the blood levels required for the onset of immunosuppressive effects are never sustainable and the possibility of the onset of systemic immunosuppressive effects is very low. Taking account of comments from the Expert Discussion, PMDA determined that the applicant's view is acceptable.

[ENDEAVOR III, ENDEAVOR IV (Reference data)]

In order to demonstrate the non-inferiority in efficacy and safety of the Endeavor Coronary Stent System to a marketed drug-eluting stent system, Cypher stent-controlled ENDEAVOR III study and TAXUS Express2 stent-controlled ENDEAVOR IV study were conducted in the US and these study results were submitted as reference data. The primary endpoint for the ENDEAVOR III study was in-segment late lumen loss at 8 months post-procedure, which was different from the primary endpoint for the ENDEAVOR IV study, TVF at 9 months post-procedure, but overall (including the primary and secondary endpoints), the chosen endpoints were comparable between the two studies.

In the ENDEAVOR III study, 323 patients received the Endeavor stent and 113 patients received the Cypher stent. In-segment late lumen loss at 8 months post-procedure was 0.36 ± 0.46 mm in the Endeavor stent group, which was significantly ($P < 0.001$) higher than 0.13 ± 0.33 mm in the Cypher stent group and the non-inferiority of the Endeavor stent to the Cypher stent could not be demonstrated. On the other hand, in the ENDEAVOR IV study, 773 patients received the

Endeavor stent and 775 patients received the TAXUS stent and TVF at 9 months post-procedure was 6.6% in the Endeavor stent group compared to 7.2% in the TAXUS stent group, demonstrating the non-inferiority of the Endeavor stent to the TAXUS stent (P = 0.0004).

Besides the clinical studies submitted as evaluation data, the results from clinical studies of the Endeavor Coronary Stent System (ENDEAVOR III, ENDEAVOR IV) and some foreign clinical studies conducted after the market launch have become available and the positioning of the Endeavor Coronary Stent System needs to be assessed appropriately under the situation where there are marketed DES products. Therefore, PMDA asked the applicant to explain the following points:

1. The non-inferiority of the Endeavor stent to a control stent was not demonstrated for the primary endpoint for the ENDEAVOR III study, in-segment late lumen loss at 8 months post-procedure and a secondary endpoint for the ENDEAVOR IV study, angiographic in-stent late lumen loss at 8 months post-procedure. Explain the degree of effectiveness and positioning of the Endeavor stent as a DES.
2. Higher rates of thrombosis and TLR etc. with the Endeavor stent have been reported from some foreign post-market registries. Taking account of these data, explain that the efficacy and safety of the Endeavor stent are clinically acceptable as compared to currently available drug-eluting stents.
3. Collect and report the latest information on stent thrombosis associated with the Endeavor stent.
4. Explain anti-platelet therapy following the implantation of the Endeavor stent.

The applicant responded as follows:
1. Although the ENDEAVOR III study could not demonstrate the non-inferiority in the primary endpoint, a secondary clinical endpoint of TLR rate (at 270 days) was 6.2% in the Endeavor stent group compared to 3.5% in the Cypher stent group and even at the 3-year follow-up, TLR rate was 7.6% in the Endeavor stent group and 4.5% in the Cypher stent group, showing no significant difference between the two groups. Also in the ENDEAVOR IV study, the Endeavor stent was shown to be inferior to the control stent for angiographic endpoints, but the non-inferiority of the Endeavor stent to the TAXUS stent was demonstrated for the primary endpoint of TVF rate. Therefore, the angiographic outcomes of the Endeavor Coronary Stent System are clinically acceptable and the product is considered to have comparable efficacy and safety to currently available DES products.

2. In post-market registries, patients were assigned to treatment groups without randomization. Therefore, the characteristics of the stents to be compared tend to confound the study results and caution is required for comparison. For example, as the Endeavor Coronary Stent System has a reputation for its deliverability, it tends to be used for more complicated lesions in foreign countries and actually, in some studies, there were differences in the angiographic profile between the Endeavor stent and compared stents. In order to adjust for such confounding factors, it is necessary to specify the target lesions and randomize patients to treatment groups in comparative clinical studies and a controlled clinical study should be conducted to appropriately determine the efficacy and safety of the product. Besides the studies submitted as evaluation data, some randomized comparative clinical studies were conducted, which have shown that the efficacy and safety of the product are clinically acceptable.

3. Thrombosis rates in the Endeavor stent group based on the pooled data from the ENDEAVOR studies are presented in Table 4. The thrombosis rates of Endeavor stent is not inferior to those of Driver stent or those previously reported with marketed DES.[2)] Therefore, the risk of thrombosis associated with the Endeavor stent is considered comparable to that associated with other DES.

Table 4 Stent thrombosis rates based on pooled data from ENDEAVOR studies (%)

Stent thrombosis (ARC Definite + Probable)	Endeavor stent (n = 2132)	Driver stent (n = 596)
Acute (within 30 days)	0.3	1.2
Late (31-360 days)	0.3	0.2
Very late (361-1440 days)	0.1	0.2

4. The optimal duration of anti-platelet therapy, especially thienopyridine therapy, following DES implantation, is unknown at present. However, the protocols of the clinical studies on the Endeavor stent required indefinite administration of aspirin and at least a 3-month administration of a thienopyridine and the subjects complied with this protocol requirement. As a result, there were no problems with stent thrombosis. Therefore, at present, the following statement will be included in the instructions for use to recommend indefinite administration of aspirin and at least a 3-month administration of a thienopyridine: “it is recommended that patients after the implantation of the Endeavor stent should receive aspirin indefinitely and a thienopyridine for a minimum of 3 months post-procedure.”

Taking account of the randomized comparative clinical studies of the Endeavor stent vs. marketed DES, PMDA considers again the positioning, efficacy, and safety of the Endeavor Coronary Stent System as follows:

The ENDEAVOR III and IV studies could not demonstrate the non-inferiority of the Endeavor stent to a control stent for angiographic late lumen loss, but there were no significant differences in TLR rate. Although late lumen loss is a suitable parameter for observing the local effects of the drug used on DES, its outcome is not necessarily directly linked with clinical therapeutic efficacy and safety. Thus, the clinical endpoints of TLR and TVF rates should be emphasized when evaluating the positioning of the Endeavor stent relative to marketed DES. TLR rate in the ENDEAVOR III study was a secondary endpoint and no adequate precision to demonstrate non-inferiority was assured, while it is noteworthy that the ENDEAVOR IV study demonstrated the non-inferiority of the Endeavor stent to the TAXUS stent for the primary endpoint of TVF rate. As to the foreign clinical registry studies, the details of the patient background, inclusion criteria, and appropriateness of treatment assignment etc. are unknown and the study results can serve as reference information, but are not adequate to evaluate the clinical positioning of the product as a DES. Based on the above, as the ENDEAVOR II study has demonstrated the superiority of the Endeavor stent over a bare metal stent and there were no clear differences in the clinical endpoints between the Endeavor stent and marketed DES, PMDA has determined that the outcomes from the clinical studies of the Endeavor Coronary Stent System are clinically acceptable. According to the currently available data, it appears that the Endeavor stent is not inferior to marketed DES in terms of thrombosis risk, but the incidences of thrombosis were low and a further investigation with many more patients should be carried out. Therefore, PMDA has determined that as with other DES products, the following condition for approval should be imposed: “Promptly report the cases of stent thrombosis associated with the use of the Endeavor stents occurring in Japan during the re-examination period and take appropriate action as needed.”

Regarding anti-platelet therapy after the implantation of the Endeavor stent, the optimal duration of thienopyridine therapy is not clearly determined at present and in the clinical studies of the Endeavor Coronary Stent System, a thienopyridine was administered for a minimum of 3 months and there were no particular problems with thrombosis. Therefore, PMDA has accepted the applicant’s opinion that administration of a thienopyridine for a minimum of 3 months post-procedure and indefinite administration of aspirin should be recommended in the instructions for use.

In addition, since long-term evaluation data obtained from many more patients are important for

assessing the efficacy and safety of the Endeavor Coronary Stent System appropriately, PMDA has determined that the following conditions for approval should be imposed: “Report annually the results of analysis of the prognosis over time for patients included in the clinical studies of the Endeavor Coronary Stent System, i.e. ENDEAVOR I, ENDEAVOR II, ENDEAVOR II-CA, ENDEAVOR III, ENDEAVOR IV, ENDEAVOR Japan, and ENDEAVOR US PK and take appropriate action as needed.” and “Report the results of analysis of the long-term prognosis over time based on the data from use-results surveys and take appropriate action as needed.”

IV. Results of Compliance Review by PMDA Concerning the Documents Appended to the Application

[Results of the document conformity audit]

A document conformity audit was conducted in accordance with the provision of Paragraph 5 of Article 14 of the Pharmaceutical Affairs Law for the documents appended to the application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted documents.

[Results of the QMS document compliance review and on-site inspection]

A compliance review was conducted in accordance with the provision of Paragraph 6 of Article 14 of the Pharmaceutical Affairs Law. As a result, PMDA concluded that there were no particular problems.

[Results of the GCP document compliance review and on-site inspection]

GCP document compliance review and on-site inspection were conducted. As a result, as there were no cases of GCP non-compliance, PMDA concluded that the studies were GCP compliant.

V. Overall Evaluation

The Endeavor Coronary Stent System is used for percutaneous coronary stenting, which is a coronary stent system inserted and deployed across the lesion to maintain the lumen patency and the stent is a drug-eluting stent coated with zotarolimus, which is expected to inhibit restenosis. In a foreign clinical study of the Endeavor Coronary Stent System (ENDEAVOR II), the incidence of the primary endpoint of target vessel failure at 9 months post-procedure was significantly reduced in the Endeavor stent group (7.9%) compared to the control group (a bare metal stent) (15.1%). The secondary efficacy endpoints of target lesion revascularization at 9 months post-procedure, target vessel revascularization at 9 months post-procedure, late loss at 8 months post-procedure, minimal lumen diameter at 8 months post-procedure, and binary restenosis rate at 8 months post-procedure were all significantly in favor of the Endeavor stent

and the safety endpoint of the incidence of Major Adverse Cardiac Events at 24 months post-procedure was also significantly reduced in the Endeavor stent group. A clinical study conducted in Japan under similar conditions (ENDEAVOR Japan) produced similar results as the foreign clinical study, demonstrating that there are no racial differences in the efficacy and safety of the Endeavor Coronary Stent System. A series of non-clinical studies were performed and in addition to the results of physicochemical tests required for metallic stents and delivery systems, as zotarolimus is an unapproved pharmaceutical product in Japan and overseas, the results from pharmacology, toxicology, and pharmacokinetic studies on the zotarolimus drug substance were submitted. In order to assure the performance of the product as a drug-eluting stent, the results of tests for identification, release rate, and content uniformity etc. of zotarolimus were submitted.

The points in the regulatory review of the Endeavor Coronary Stent System were as follows: (a) Appropriately assess the risk associated with zotarolimus, taking into account that zotarolimus is not approved as a pharmaceutical product in Japan and overseas, (b) Appropriately evaluate the positioning of the Endeavor Coronary Stent System under the situation where there are marketed DES products.

The PMDA's conclusions, taking account of discussions with the expert advisors, are as follows:

1. Although zotarolimus is an analog of sirolimus, as it has not been developed as a pharmaceutical product, there is no information about blood concentrations at which it exerts systemic pharmacological effects as a drug or adverse drug reactions to the doses producing systemic pharmacological effects. Thus, it is necessary to estimate the physiological activity profile of zotarolimus based on comparison of the pharmacological effects and of the results from animal studies etc. between zotarolimus and sirolimus. Considering from this point of view, adverse drug reactions etc. associated with zotarolimus used on the Endeavor Coronary Stent System are not a major problem, because zotarolimus is considered to inhibit neointimal proliferation via the same mechanism of action as sirolimus; according to the immunosuppressive findings from zotarolimus toxicity studies, zotarolimus is expected to exert its immunosuppressive effects over a dose range that is not substantially different from that of sirolimus; and there were no findings of safety concern in zotarolimus toxicity studies and animal model studies, and based on the results of measurement of blood drug concentrations. However, as the clinical studies have limitations in terms of the duration of evaluation and the number of cases evaluated, as with other DES products, the following conditions for approval should be imposed: "Report annually the results of analysis of the prognosis over time for

patients included in the clinical studies of the Endeavor Coronary Stent System, i.e. ENDEAVOR I, ENDEAVOR II, ENDEAVOR II-CA, ENDEAVOR III, ENDEAVOR IV, ENDEAVOR Japan, and ENDEAVOR US PK and take appropriate action as needed." and "Report the results of analysis of the long-term prognosis over time based on the data from use-results surveys and take appropriate action as needed."

2. The ENDEAVOR II study has demonstrated the superiority of the Endeavor stent over a bare metal stent. In the randomized comparative clinical studies of the Endeavor Coronary Stent System, even when the non-inferiority in angiographic endpoints could not be demonstrated, there were no major differences in clinical endpoints between marketed DES and the Endeavor stent, and no results denying the efficacy and safety of the Endeavor stent were obtained. Therefore, the outcomes from the clinical studies of the Endeavor Coronary Stent System have been determined to be clinically acceptable. However, since appropriate action against stent thrombosis including late thrombosis is essential for DES in terms of post-marketing safety measures and long-term evaluation data obtained from many more patients are important for assessing the efficacy and safety of the Endeavor Coronary Stent System more appropriately, the following condition for approval, in addition to the above-mentioned two conditions, should be imposed: "Promptly report the cases of stent thrombosis associated with the use of the Endeavor stents occurring in Japan during the re-examination period and take appropriate action as needed."

Based on the above results, PMDA has concluded that the product may be approved for the intended use as described below. However, as it is important to collect information on the Endeavor Coronary Stent System by carefully observing the long-term prognosis and the occurrence of stent thrombosis, and adverse drug reactions associated with zotarolimus, the following conditions for approval need to be imposed.

[Intended use]
Treatment of patients with symptomatic ischemic heart disease due to *de novo* coronary artery lesions with a reference vessel diameter ranging from 2.5 to 3.5 mm and lesion length $\leq$ 27 mm

[Conditions for approval]
1. Report annually the results of analysis of the prognosis over time for patients included in the clinical studies of the Endeavor Coronary Stent System, i.e. ENDEAVOR I, ENDEAVOR II, ENDEAVOR II-CA, ENDEAVOR III, ENDEAVOR IV, ENDEAVOR Japan, and ENDEAVOR US PK and take appropriate action as needed.

2. Report the results of analysis of the long-term prognosis over time based on the data from use-results surveys and take appropriate action as needed.
3. Promptly report the cases of stent thrombosis associated with the use of the Endeavor stents occurring in Japan during the re-examination period and take appropriate action as needed.

As the Endeavor Coronary Stent System is a new performance medical device, the appropriate re-examination period should be 3 years. The product is not classified as a biological product or a specified biological product.

The application should be deliberated at the Committee on Medical Devices and In-vitro Diagnostics.

[References]
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