Report on the Deliberation Results

September 16, 2008
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

[Brand name]	Thaled Capsule 100
[Non-proprietary name]	Thalidomide (JAN*)
[Applicant]	Fujimoto Pharmaceutical Corporation
[Date of application]	August 8, 2006

[Results of deliberation]
In the meeting held on August 27, 2008, the Second Committee on New Drugs concluded that the product may be approved and decided to place the results of the deliberation before the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

In addition, the following conclusions were reached: the product is not classified as a biological product or a specified biological product; the re-examination period is 10 years; and both the drug substance and the drug product are classified as poisonous drugs.

It was decided that "PRECAUTIONS" in the package insert are to include a statement to the effect that each prescription for the product should be for 2 weeks, as a general rule.

The product is approved under the following 3 conditions.

1. Strict and appropriate measures should be taken to assure that the product is administered only to patients in whom it is indicated, under the supervision of a physician with knowledge and experience at a medical institution where adequate facilities for the treatment of emergencies are available, after each patient or his/her family members have been provided with written information on the efficacy and risks of the treatment and have given written informed consent in advance.

2. Because of the extremely limited number of patients investigated in the Japanese clinical study, a drug use investigation should be carried out on all patients treated with the product after marketing until data has been accumulated from a certain number of patients, and the results should be published periodically. After a certain period of time has passed since the marketing, data related to the safety and efficacy of the product should be collected expeditiously, such as by conducting appropriate clinical studies, based on the information obtained at each time point and on the comments of medical experts and biostatisticians, and appropriate measures should be taken to assure proper use of the product.

3. Appropriate implementation of safety management measures (proposed)
(Safety management measures will be discussed at the "Review committee on the safety management for the prevention of recurrence of Thalidomide-related damage" and at the Committee on Drug Safety).

**Japanese Accepted Name (modified INN)*

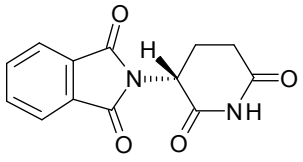
Review Report

August 11, 2008
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Thaled Capsule 100
[Non-proprietary name]	Thalidomide
[Applicant]	Fujimoto Pharmaceutical Corporation
[Date of application]	August 8, 2006
[Dosage form/Strength]	Capsules, each containing 100 mg of Thalidomide
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



and its enantiomer

Molecular formula: $C_{13}H_{10}N_2O_4$
Molecular weight: 258.23
Chemical name: 2-[(3*RS*)-2,6-dioxopiperidin-3-yl]isoindoline-1,3-dione

[Items warranting special mention]	Orphan drug (February 8, 2005. Designation No. [17 *Yaku*] No. 178)
[Reviewing office]	Office of New Drug I

Review Results

August 11, 2008

[Brand name]	Thaled Capsule 100
[Non-proprietary name]	Thalidomide
[Applicant]	Fujimoto Pharmaceutical Corporation
[Date of application]	August 8, 2006
[Dosage form/Strength]	Capsules, each containing 100 mg of Thalidomide

[Results of review]
The Pharmaceutical and Medical Devices Agency has concluded that the submitted data and information demonstrated the efficacy and safety of the product for use in the treatment of "relapsed or refractory multiple myeloma."

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indications and dosage and administration under the following conditions.

Safety management measures are being addressed separately.

[Indications]
Relapsed or refractory multiple myeloma

[Dosage and administration]
The usual adult dosage for oral use is 100 mg of Thalidomide once daily before bedtime. The dosage may be increased or decreased, according to the patient's condition, up to a maximum of 400 mg per day.

[Conditions for approval]
1. Strict and appropriate measures should be taken to assure that the product is administered only to patients in whom it is indicated, under the supervision of a physician with knowledge and experience at a medical institution where adequate facilities for the treatment of emergencies are available, after each patient or his/her family members have been provided with written information on the efficacy and risks of the treatment and have given written informed consent in advance.

2. Because of the extremely limited number of patients investigated in the Japanese clinical study, a drug use investigation should be carried out on all patients treated with the product after marketing until data has been accumulated from a certain number of patients, and the results should be published periodically. After a certain period of time has passed since the marketing, data related to the safety and efficacy of the product should be collected expeditiously, such as by conducting appropriate clinical studies, based on the information obtained at each time point and on the comments of medical experts and biostatisticians, and appropriate measures should be taken to assure proper use of the product.

Review Report (1)

July 10, 2008

I. Overview of the Product

[Brand name]	Thaled Capsule 100
[Non-proprietary name]	Thalidomide
[Applicant]	Fujimoto Pharmaceutical Corporation
[Date of application]	August 8, 2006
[Dosage form/Strength]	Capsules, each containing 100 mg of Thalidomide
[Proposed indications]	Multiple myeloma (to be used only when conventional treatment is not sufficiently effective)
[Proposed dosage and administration]	The usual adult dosage for oral use is 100 mg of Thalidomide once daily before bedtime. The dosage may be increased or decreased, according to the patient's age and symptoms, up to a maximum of 400 mg per day.
[Items warranting special mention]	Orphan drug (February 8, 2005. Designation No. [17 *Yaku*] No. 178)

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

The data and information submitted by the applicant and the applicant's responses to the questions from the Pharmaceuticals and Medical Devices Agency (PMDA) are as follows.

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

1.1 Overview of the product

Thalidomide is a glutamic acid derivative developed in 1953 by Ciba AG (currently Novartis Pharma AG) in Switzerland. Subsequently, Chemie Grünenthal GmbH (currently Grünenthal GmbH) in the former West Germany noticed that Thalidomide had a sedative action and began marketing Thalidomide, starting in 1957, as a sleep-inducing agent and a tranquilizer in the former West Germany, which was followed by 46 countries worldwide, the exception being the US. In Japan, Dainippon Pharmaceutical Co., Ltd. (currently Dainippon Sumitomo Pharma Co., Ltd.) conducted clinical development of Thalidomide and, in 1957, filed an application for a manufacturing license for Thalidomide as an agent for treating insomnia, etc. The marketing of Thalidomide in Japan was started in 1958 (brand name, Isomin), and the oral combination drug containing Thalidomide (brand name, Proban-M, etc.) was marketed starting in 1960 as a therapeutic agent for hyperchlorhydria, gastritis, and peptic ulcer. However, due to reports that the clinical use of Thalidomide was associated with teratogenicity (Thalidomide embryopathy) in Japan and overseas, cessation of the shipment of Thalidomide and recall were started in 1962 in Japan, followed by cancellation of the approval of Thalidomide under the Pharmaceutical Affairs Law.

Then, triggered by a report in 1965 by a physician in Israel that Thalidomide inhibited erythema nodosum leprosum (*Clin Pharmacol Ther.* 1965;6:303-306), various clinical investigations were conducted in Japan as well as overseas on the effect of Thalidomide in autoimmune diseases, malignant tumors, etc., based on the pharmacological actions of Thalidomide such as the inhibition of angiogenesis and the inhibition of tumor necrosis factor (TNF)-α production. As regards multiple myeloma, results of a clinical study were published in 1965 (*Clin Pharmacol Ther.* 1965;6:292-297). Results of a clinical study in patients with refractory multiple myeloma were also reported (*N Engl J Med.* 1999;341:1565-1571, etc.).

Reported pharmacological actions of Thalidomide other than its sedative action include inhibition of angiogenesis, inhibition of cytokine productions such as that of TNF-α, immunomodulation, inhibition of the expressions of cell adhesion molecules, induction of apoptosis, and inhibition of cell growth. Thalidomide is considered to inhibit the growth of myeloma cells via a combination of these actions.

1.2 History of development of Thalidomide

The summary report of the research supported by the Health and Labour Sciences Research Grant in 2002 entitled "Investigations on the use state and proper use of privately-imported unapproved drugs" (chief investigator, Naokata Shimizu) (2002, document No. 200200123A) outlined the current status of the use of privately-imported Thalidomide in Japan and available measures for the safe use of Thalidomide. Following said recommendation, the PFSB/SD Notification No. 0919002 issued by the Director of the Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 19, 2003, entitled "The report of the investigations on the use state and safe use of Thalidomide" was issued. This notification recommends that the clinical use of Thalidomide be under fully controlled conditions as a clinical study, as defined in the Pharmaceutical Affairs Law. In response to the request of the Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, the Japanese Society of Clinical Hematology established a standard guideline for the safe use of Thalidomide, notification of which was provided as the PFSB/SD Notification No. 1210001 issued by the Director of the Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated December 10, 2004, entitled "Guideline for the appropriate use of Thalidomide in the treatment of multiple myeloma." In addition, the issue of Thalidomide was discussed on January 24, 2005 at the first meeting of the Investigational Committee for Usage of Unapproved Drugs, a committee established by the Minister of Health, Labour and Welfare, and the conclusion was reached that clinical studies should be started as soon as possible.

In [redacted], the applicant began the investigation on the formulation of Thalidomide for its clinical development in Japan, and conducted clinical studies starting in [redacted], [redacted] in Japan involving patients with multiple myeloma using capsules with a formulation different from that of the products marketed in foreign countries. The present application for approval of Thalidomide was filed based on the results obtained from these clinical studies.

Safety management of the Thalidomide product (product submitted for registration) after marketing in Japan is being addressed separately.

Whereas development of the product submitted for registration has not been carried out in foreign countries, Thalidomide products with formulations different from the proposed product have been approved in the following countries, with multiple myeloma as the indication for use, as of May 2008.

In the US, a Thalidomide product (capsule formulation) manufactured by Celgene Corporation was approved in May 2006 with the following indication: "THALOMID (Thalidomide) in combination with dexamethasone is indicated for the treatment of patients with newly diagnosed multiple myeloma," and its safety is controlled by the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program.

The Thalidomide product (capsule formulation) of Pharmion Corporation was approved in October 2003 in Australia with the following indication: "the treatment of multiple myeloma after failure of standard therapies," followed by approval in New Zealand, Turkey, Israel, South Africa, Thailand, and South Korea by October 2007. In these countries, the distribution of the drug is controlled according to the Pharmion Risk Management Program (PRMP) that was established by referring to the S.T.E.P.S.

In the EU, the Thalidomide product (capsule formulation) of Pharmion Corporation was approved in April 2008 through the centralized procedure with the following indication: "Thalidomide Pharmion in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy," and is controlled for safety under the Thalidomide Pharmion Pregnancy Prevention Programme.

Thalidomide products marketed in Mexico and Brazil have been approved for erythema nodosum leprosum but not for multiple myeloma.

2. Data relating to quality

2. 1) Drug substance

2. 1).(1) Manufacturing process

The drug substance Thalidomide is manufactured in a total of 7 steps using [redacted] and [redacted] as the starting materials.

Step 1: [redacted] and [redacted] to [redacted], [redacted] after [redacted].
Step 2: Add [redacted] to [redacted] obtained in Step 1 and the remaining [redacted], and stir the mixture. Then [redacted] the mixture, and after [redacted], [redacted] of [redacted] is obtained.
Step 3: [redacted] of [redacted] and [redacted] of [redacted], to which add [redacted]. After [redacted], add [redacted] and [redacted] after [redacted], to obtain [redacted] of 2-[(3*RS*)-2,6-dioxopiperidin-3-yl]isoindoline-1,3-dione.
Step 4: Dissolve [redacted] of 2-[(3*RS*)-2,6-dioxopiperidin-3-yl]isoindoline-1,3-dione in [redacted], and add [redacted] to the solution. [redacted], and add [redacted] to [redacted], [redacted] to obtain crystals. Dry the crystals thus obtained under reduced pressure to obtain 2-[(3*RS*)-2,6-dioxopiperidin-3-yl]isoindoline-1,3-dione.
Step 5: Place 2-[(3*RS*)-2,6-dioxopiperidin-3-yl]isoindoline-1,3-dione in [redacted] and pack in [redacted].
Step 6: [redacted] 2-[(3*RS*)-2,6-dioxopiperidin-3-yl]isoindoline-1,3-dione.
Step 7: Place [redacted] 2-[(3*RS*)-2,6-dioxopiperidin-3-yl]isoindoline-1,3-dione in [redacted] and pack in [redacted].

Steps [redacted] through [redacted] and [redacted] are defined as critical process steps, and [redacted] of [redacted] and [redacted] 2-[(3*RS*)-2,6-dioxopiperidin-3-yl]isoindoline-1,3-dione are controlled as key intermediates by in-process control tests.

Background of development of the manufacturing process

In the initial stage of the development, the applicant contracted out the manufacture of Thalidomide to [redacted]. However, because of the difficulty to [redacted] in this company, the contractor for the manufacture of Thalidomide was changed to [redacted] in [redacted]. However, there is no change in [redacted] because the method of synthesis [redacted] was [redacted] to [redacted] and [redacted] at [redacted].

2. 1).(2) Characteristic features

General properties

Investigations have been conducted on the physicochemical properties of Thalidomide, including physical description, melting point, solubility, thermal analysis, hygroscopicity, dissociation constant (pKa), partition coefficient, X-ray powder diffraction, crystalline polymorphism, optical rotation, degradation products, and stability in aqueous solution.

Thalidomide occurs as a white crystalline powder with a melting point of 277°C. It is freely soluble in dimethylsulfoxide, slightly soluble in acetonitrile, acetone, ethyl acetate, and acetic acid (100), very slightly soluble in methanol and ethanol (99.5), and practically insoluble in water. No differences are observed in the solubility in solutions with various pH values; Thalidomide is

practically insoluble. A sharp endothermic peak due to melting of the crystals was observed at [redacted]°C. No hygroscopicity was observed. Since Thalidomide is readily hydrolyzed in alkaline solutions, pKa was calculated based on the theoretical equation. As a result, pKa was calculated to be [redacted]. No partition coefficient could be obtained because Thalidomide was hydrolyzed in the test solution of pH [redacted], whereas in an acidic pH range, Thalidomide was more apt to be distributed in the organic layer. X-ray powder diffraction confirmed that Thalidomide was a crystalline powder and that it was present as 2 crystalline polymorphic forms: [redacted] form and [redacted] form. The [redacted] form is obtained by recrystallization from [redacted], [redacted], or [redacted], and the [redacted] form is obtained by recrystallization in [redacted] solution of [redacted]. Thalidomide exists in the [redacted] form, which can be differentiated from the other form by the pattern of X-ray powder diffraction and by the infrared spectrum. Because of its racemic nature, Thalidomide does not show optical rotation. Hydrolysis products were identified by two-dimensional paper chromatography, from which the degradation pathway has been estimated. Regarding the stability in aqueous solution, it was found that the degradation rate increased as the pH increased.

Determination of structure
The chemical structure of Thalidomide is supported by elementary analysis, ultraviolet spectrum, infrared spectrum, nuclear magnetic resonance spectrum (^{1}H-NMR, ^{13}C-NMR), and mass spectrum.

2. 1).(3) Control of drug substance
The structural formula, molecular formula, content of Thalidomide, physical description (appearance, solubility, optical rotation, melting point), identification (ultraviolet-visible spectrophotometry, infrared spectrophotometry), purity (heavy metals, related substances [[redacted] related substance, [redacted] related substance]), water content, residue on ignition, and assay (liquid chromatography) are set for the specifications for Thalidomide.

2. 1).(4) Stability of drug substance
The stability of Thalidomide was evaluated using 3 lots manufactured on a scale of not less than 10% of the commercial manufacturing scale according to the synthetic method used for the commercial manufacturing. The test conditions in the stability studies were as follows.

Test		Temperature (°C)	Humidity (%RH)	Light	Storage container	Storage period
Long-term testing		25 ± 2	60 ± 5	Dark place	Polyethylene bag (heat-sealed)	24 months
Accelerated testing		40 ± 2	75 ± 5	Dark place	Polyethylene bag (heat-sealed)	6 months
Stress testing	Temperature	50 ± 2	-	Dark place	Brown vial (tightly closed)	6 months
		60 ± 2	-	Dark place	Brown vial (tightly closed)	6 months
	Humidity	25 ± 2	90	Dark place	Brown vial (open)	6 months
	Light	25 ± 2	60 ± 5	Fluorescent lamp 2000 lx/h	Petri dish (polyvinylidene chloride film)	1.344 million lx·h

No time-course changes were observed under any of the test conditions.
Based on the above results, the proposed re-test period for Thalidomide is 36 months when packed in polyethylene bag [redacted] and then in sealed air-tight [redacted] and stored at room temperature, according to the PFSB/ELD Notification No. 0603001 dated June 3, 2003, "Revision of the guidelines on stability testing." The long-term testing will be continued for up to 39 months.

2. 2) Reference standard

Purification process

Dissolve Thalidomide in [redacted], and add [redacted] to the solution. Cool the [redacted] thus obtained to room temperature. Isolate the crystals, wash them with [redacted], and dry the crystals in a desiccator (reduced pressure, phosphorus oxide [V], [redacted]°C) for [redacted] hours. Repeat the procedure, if necessary.

2. 2).(1) Specifications

In addition to compliance with the specifications for the drug substance, the following are set for the specifications for the reference standard of Thalidomide: the drug substance with an assay value of 99.0% to 101.0% should be dried for [redacted] hours in a desiccator (reduced pressure, phosphorus oxide [V], [redacted]°C); and infrared spectrum (wave numbers defined) should be controlled as identification.

2. 3) Drug product

2. 3).(1) Drug product and formulation

The proposed product is a capsule formulation, in which each capsule contains 100 mg of Thalidomide with the following formulation.

Purpose of ingredient	Specification	Name of component	Content (mg)
Active ingredient	Separate specification	Thalidomide	100
Vehicle	Japanese Pharmacopeia	Anhydrous lactose	[redacted]
[redacted]	Japanese Pharmacopeia	Microcrystalline cellulose	[redacted]
[redacted]	Japanese Pharmacopeia	Low substituted hydroxypropylcellulose	[redacted]
[redacted]	Japanese Pharmacopeia	Povidone K30	[redacted]
[redacted]	Japanese Pharmacopeia	Stearic acid	[redacted]
[redacted]	Japanese Pharmacopeia	Light anhydrous silicic acid	[redacted]
-	Japanese Pharmacopeia	Capsule	1 capsule

2. 3).(2) Development of drug product

Because of the very low water solubility of the active ingredient, Thalidomide, dissolution of the drug product was low, raising a concern about absorption into the body. Therefore, in order to improve the dissolution, Thalidomide was [redacted] into [redacted]. Thalidomide is known to show 2 crystalline polymorphic forms: [redacted] form and [redacted] form, while both Thalidomide [redacted] and its capsule formulation exist in the [redacted] form. The proposed product is also based on the crystals of [redacted]-form Thalidomide.

2. 3).(3) Manufacturing process

The drug product is manufactured in the following 5 steps:

Step 1: Place Thalidomide, anhydrous lactose, microcrystalline cellulose, [redacted], and [redacted] in [redacted] and mix. Then, [redacted] [redacted] for [redacted], [redacted] and [redacted].

Step 2: Transfer [redacted] manufactured in Step 1 into a vessel, and add [redacted] and [redacted]. Mix the contents, followed by [redacted].

Step 3: Fill capsules with the [redacted] manufactured in Step 2.

Step 4: After sealing the capsules in PTP sheets using a PTP packaging machine, pack them in cartons.

Step 5: Store and perform inspection and testing.

Steps [redacted] through [redacted] are defined as the critical process steps and are controlled by in-process control tests.

2. 3).(4) Control of drug product

The content of Thalidomide, physical description (appearance [capsule/contents]), identification (ultraviolet-visible spectrophotometry, thin-layer chromatography, liquid chromatography), uniformity of dosage units (mass variation), dissolution, and assay (liquid chromatography) are set for the specifications for the drug product.

2. 3).(5) Stability of drug product

Results of stability studies, performed on 3 lots of drug products manufactured according to the proposed formulation, by the process reflecting the commercial manufacturing, and on a scale of not less than 10% of the commercial manufacturing scale, were submitted. The test conditions in the stability studies were as follows.

Test		Temperature (°C)	Humidity (%RH)	Light	Storage container	Storage period
Long-term testing		25 ± 2	60 ± 5	Dark place	PTP (PVC/AL) Carton	24 months
Accelerated testing		40 ± 2	75 ± 5	Dark place	PTP (PVC/AL) Carton	6 months
Stress testing	Temperature	50 ± 2	-	Dark place	PTP (PVC/AL) Carton	6 months
		60 ± 2	-	Dark place	PTP (PVC/AL) Carton	6 months
	Humidity	25 ± 2	90	Dark place	PTP (PVC/AL) Carton	6 months
	Light	25 ± 2	60 ± 5	Fluorescent lamp 2000 lx/h	Petri dish (polyvinylidene chloride film)	1.344 million lx·h

PVC/AL: Polyvinyl chloride/aluminum foil

Results of the long-term testing demonstrated that water content changed slightly (up to [redacted]% from baseline), whereas there were no changes in the other attributes tested.

Results of the accelerated testing demonstrated that water content changed slightly (up to [redacted]% from baseline), whereas there were no changes in the other attributes tested.

Results of the stress testing (temperature) demonstrated time-course decreases in water content ([redacted]% at 50°C and [redacted]% at 60°C from baseline) and a time-course decrease in the dissolution rate, at 60°C in particular ([redacted]% from baseline).

Results of the stress testing (humidity) demonstrated time-course increases in water content ([redacted]% from baseline) and time-course increases in assay value ([redacted]% from baseline).

Results of the stress testing (light) demonstrated that the drug product was stable when exposed to light.

On the basis of the above results showing the susceptibility of the drug product in PTP packages to humidity, the proposed expiration period for the drug product is 36 months when secondarily packaged in an aluminum laminate film to protect it from humidity and stored at room temperature, according to the PFSB/ELD Notification No. 0603001 dated June 3, 2003, "Revision of the guidelines on stability testing." The long-term testing will be continued for up to 39 months.

Outline of the review by the PMDA
Based on the data submitted and on the following discussion, the PMDA concluded that there was no problem with the quality of the drug substance or the drug product.

The PMDA considered the proposed dissolution test for the drug product to be inappropriate for the following reasons and asked the applicant to reconsider the test conditions.

- Although the solubility of Thalidomide in the 1st fluid for the dissolution test (JP) containing [redacted]% polysorbate 80 is [redacted] μg/mL, the volume of the test solution is 900 mL.

- The sampling time point is set at 120 minutes after the start of the test, the time point at which saturation is considered to have been reached.

- It appears that the conditions for the dissolution test have not been fully investigated.

The applicant responded as follows:
In order to accurately differentiate the drug product used in clinical studies, test conditions were investigated employing the drug product manufactured using [redacted] drug substance, the drug product manufactured without adding [redacted], which is [redacted], the drug product that had been stored under stress conditions, and other drug products. Based on the results obtained from this investigation, the sampling time point has been changed from 120 minutes after the start of the test to 30 minutes after the start of the test, and the dissolution rate has been changed to "not less than [redacted]%."

The PMDA accepted the applicant's response, assuming that the quality of the drug product would be appropriately evaluated under the revised conditions for the dissolution test.

3. Non-clinical data
3.1 Pharmacology data
3.1.A *Summary of the submitted data*
No non-clinical evaluation data was submitted with the present application. Instead, the following 28 publications were submitted as reference data.

The publications submitted as reference data were all selected by the applicant from among 52 reports on non-clinical pharmacology and 13 reports on safety pharmacology, all of which were on multiple myeloma, published in academic journals, among 9751 reports (excluding duplicates) retrieved as of March 23, 2006, using the key word "thalidomide" from MEDLINE, EMBASE, and *Igaku Chuo Zasshi* (*Japana Centra Revuo Medicina*).

Primary pharmacodynamics (17 reports)
Graefes Arch Clin Exp Ophthalmol. 1998;236:461-466, *Proc Natl Acad Sci U S A.* 1994;91:4082-4085, *Neoplasma.* 2005;52:175-181, *J Neurooncol.* 2003;64:193-201, *Blood.* 2003;102:3340-3348, *J Exp Med.* 1991;173:699-703, *J Exp Med.* 1993;177:1675-1680, *J Immunol.* 2002;168:2644-2651, *Leukemia.* 2001;15:1950-1961, *Cell Mol Biol (Noisy-le-grand).* 2001;47:1105-1114, *Blood.* 2001;98:210-216, *J Immunol.* 1999;163:380-386, *J Leukoc Biol.* 2002;72:939-945, *J Exp Med.* 1998;187:1885-1892, *Blood.* 2000;96:2943-2950, *Vascul Pharmacol.* 2005;43:112-119, *Blood.* 2002;99:4525-4530.

Safety pharmacology (11 reports)
Int J Toxicol. 1999;18:337-352, *Arzneimittelforschung.* 1982;32:613-620, *J Pharmacol Exp Ther.* 1961;134:60-68, *Br J Pharmacol Chemother.* 1960;15:111-116, *J Pharmacol Exp Ther.* 1977;203:240-251, *Life Sci.* 1964;3:721-724, *Arzneimittelforschung.* 1979;29:1146-1150, *Eur J*

Pharmacol. 2000;391:97-103, *Nippon Yakurigaku Zasshi.* 1973;69:599-619, *Toxicol Sci.* 2001;59:160-168 (GLP study), *Cardiovasc Toxicol.* 2004;4:29-36.

The applicant presented the following discussion on the pharmacological actions of Thalidomide based on the findings reported in the above publications.

The modes of action of Thalidomide in multiple myeloma include the following:

a. Inhibition of angiogenesis mediated by VEGF, bFGF, etc.
b. Inhibition of cytokine (such as TNF-α and IL-6) productions, inhibition of activation of transcription factor NF-κB, and inhibition of cell adhesion molecule expressions
c. Immunomodulation via the growth of NK cells and cytotoxic T cells
d. Apoptosis induction and growth inhibition of multiple myeloma cells, etc., mediated by caspase 8, Bcl-2, and COX-2.

It appears that Thalidomide exhibits activity against multiple myeloma [Note by PMDA: Inhibition of the growth of multiple myeloma cells] via the concerted actions of these modes. Since all of the above studies were conducted using human-derived cells, similar effects are expected when the drug is administered to humans.

In safety pharmacology studies, Thalidomide produced suppression of the central nervous system, inhibition of acetylcholine- and histamine-induced contraction of isolated ileum preparations, slight decreases in the heart rates of isolated hearts, prolongation of the QTc interval, and positive inotropic and lusitropic effects (Thalidomide had no effect on isolated rabbit hearts [at 10 μg/mL]).

3.1.B *Outline of the review by the PMDA*

Regarding the inclusion criteria for the study reports submitted as reference data, the applicant gave the following explanation.

As a result of the literature retrieval, a total of 52 reports on primary pharmacodynamics were selected for evaluation. Study reports that did not address any of the following 4 items, the major pharmacological actions of Thalidomide as judged by the applicant, were not included in the reference data (reason for exclusion: although pharmacological actions other than those regarded by the applicant as the major pharmacological actions of Thalidomide were reported, they were not described in multiple reports, and were therefore judged by the applicant to be less reliable).

a. Inhibition of angiogenesis
b. Inhibition of cytokine productions and inhibition of cell adhesion molecule expressions
c. Immunomodulation
d. Apoptosis induction and cell growth inhibition

For safety pharmacology, a study that used only one animal per group and another study that used Thalidomide only at a single dose level were excluded from the reference data.

In the present application, the PMDA did not evaluate the submitted data on non-clinical pharmacology because the data were submitted for reference purposes. The PMDA understands that the publications submitted as reference data are limited to those reports on the major pharmacological actions of Thalidomide, as judged by the applicant.

Given the clinical track record of Thalidomide, the PMDA considers the drug to potentially be clinically useful for the treatment of multiple myeloma. Although various pharmacological actions have been reported, the target molecule of Thalidomide has not been definitely identified, and thus requires further investigation. The applicant reported having searched for reports on the

mechanism by which tumors develop resistance to Thalidomide but could not find relevant study reports. Therefore, the mechanism of resistance development is unclear at present. Thus, elucidation of the mechanism of resistance development is also an issue which needs to be addressed in future studies.

For safety, the publications submitted as reference data demonstrated a significant decrease in the duration of wakefulness following oral administration of Thalidomide at ≥ 300 mg/kg in rabbits, at ≥ 16 mg/kg in rats, and at ≥ 4 mg/kg in cats (*Nippon Yakurigaku Zasshi.* 1973;69:599-619, *J Pharmacol Exp Ther.* 1977;203:240-251). The PMDA therefore considers it advisable to exercise caution against the possible occurrence of somnolence, etc., in clinical use.

3.2 Pharmacokinetic data

3.2.A *Summary of the submitted data*

No evaluation data on non-clinical pharmacokinetics (PK) studies has been submitted. Instead, the following publications were submitted as reference data.

The publications submitted as reference data were all reviewed and selected by the applicant as non-clinical PK data on THAL from among 45 PK reports published in academic journals among 9751 reports (excluding duplicates) retrieved as of March 23, 2006, using the key word "thalidomide" from MEDLINE, EMBASE, and *Igaku Chuo Zasshi* (*Japana Centra Revuo Medicina*) (absorption, 7 reports; distribution, 5 reports; metabolism, 6 reports; excretion, 2 reports; pharmacokinetic drug interactions, 1 report; 21 reports in total).

Absorption: *Clin Cancer Res.* 2004;10:5949-5956, *J Pharmacol Exp Ther.* 1968;160:201-211, *Teratology.* 1971;4:75-85, *Birth Defects Res B Dev Reprod Toxicol.* 2004;71:1-16, *J Pharmacol Exp Ther.* 1970;173:265-269, *Cancer Chemother Pharmacol.* 2006;57:599-606, *J Chromatogr B Analyt Technol Biomed Life Sci.* 2003;785:165-173.

Distribution: *Proc Soc Exp Biol Med.* 1964;116:512-516, *J Pharm Pharmacol.* 1966;18:46-48, *Biochem J.* 1967;104:565-569, *Chirality.* 1998;10:223-228, *Proc Natl Acad Sci U S A.* 1996;93:7552-7556.

Metabolism: *Clin Cancer Res.* 2003;9:1680-1688, *Br J Pharmacol.* 1965;25:338-351, *J Pharmacol Exp Ther.* 2004;310:571-577, *J Pharm Pharmacol.* 1998;50:1409-1416, *Clin Cancer Res.* 2002;8:1964-1973, *Arch Dermatol Res.* 1994;286:347-349.

Excretion: *Proc Soc Exp Biol Med.* 1962;109:511-515, *Toxicol Sci.* 2004;81:379-389.

Pharmacokinetic drug interactions: *J Biochem Mol Toxicol.* 2000;14:140-147.

On the basis of the findings reported in the above publications, the applicant presented the following discussion.

3.2.A.1) Absorption

The following findings, which suggest that the poor solubility of Thalidomide affects absorption, have been reported.

a. When a 2 or 20 mg/kg dose of Thalidomide was orally administered to mice, AUC increased in proportion to the dose, whereas the increase in C_{max} was less than that expected from the linear relationship to the proportion administered. Also, a delay in T_{max} and an increase in $t_{1/2}$ were observed with the dose increase.

b. The urinary excretion rate during the 48 hours after oral administration of 10 mg/kg of Thalidomide to rats was approximately 2 times higher when the drug was administered in dimethylsulfoxide:propylene glycol (1:1) solution than the value obtained when the drug was administered in an aqueous suspension.
c. The plasma Thalidomide concentration following oral administration of 50 mg/kg of Thalidomide to rabbits was lower when the drug was administered in a gelatin capsule than when administered as a carboxymethyl cellulose suspension.

In the *in vitro* study using Caco-2 cells, the membrane permeability of Thalidomide was not affected by verapamil, a P-gp inhibitor, and Thalidomide showed dose-dependent permeability. Based on these results, the applicant considers Thalidomide to be well absorbed. The applicant also considers aggregation of Thalidomide in the gastrointestinal tract, due to the hydrophobicity of Thalidomide, to possibly reduce the dissolution rate, thereby contributing to effects on the absorption rate and absorption ratio of Thalidomide.

Since the plasma Thalidomide concentrations following repeated doses in rabbits and rats were comparable to those observed following a single dose, the applicant has concluded that repeated doses of Thalidomide are unlikely to cause its accumulation.

3.2.A.2) Distribution

The following findings related to the tissue distribution of Thalidomide have been reported.

When radiolabeled Thalidomide was orally administered to mice, high radioactivity was detected in the gastrointestinal tract, liver, and kidneys, whereas the extents of distribution were similar in other tissues.

After the administration of Thalidomide to rats and monkeys, the drug was detected in the brains of these animals.

When Thalidomide was orally administered to pregnant mice, rabbits, and monkeys, exposure of the fetuses to Thalidomide was observed.

Thalidomide was detected in the seminal fluid of male rabbits at a third to a half of the plasma concentration.

Thalidomide was bound to human plasma albumin or α1-acid glycoprotein and transferred to red blood cells. The plasma protein binding rates of the (+)-(R)-form and the (-)-(S)-form of Thalidomide were 55% and 66%, respectively.

3.2.A.3) Metabolism

3.2.A.3).(1) Metabolic pathway

On the basis of the following findings on the metabolism of Thalidomide, the applicant considers that there are species differences in the hydrolysis and hydroxylation reactions of Thalidomide and that the drug undergoes little or no hydroxylation in humans, as judged by the concentration of the hydroxylated metabolites detected. The applicant also claims that non-enzymatic hydrolysis is the major metabolic reaction of Thalidomide and that the contribution of CYP450 to the metabolism of Thalidomide is minimal.

Various hydroxides and hydrolysates were observed as Thalidomide metabolites in liver microsomes. These hydrolysates were shown to be products of non-enzymatic reactions in humans and mice, with the amounts produced being comparable between the 2 species, whereas a larger amount of hydrolysates was produced in rabbits, suggesting the involvement of enzymes in the hydrolysis of Thalidomide in this animal species. In contrast, hydroxides were produced in a larger

amount in the liver microsomes of mice than in those of rabbits. The hydrolysates and the hydroxides were produced in similar amounts in mice, whereas hydrolysates were produced in a higher amount than the hydroxides in rabbits.

In a study using liver microsomes and the S9 fraction, 5-hydroxylated and 5'-hydroxylated metabolites were observed as the hydroxylated metabolites of Thalidomide. The amounts of these hydroxylated metabolites produced in humans were very small, being lower than the amounts in mice, rats, rabbits, and dogs. In rats, CYP2C6 and 2C11 were shown to be involved in the hydroxylation reaction, and there was a gender difference in the hydroxylation reaction.

No consensus has been reached among publications regarding the metabolites in plasma and urine after administration of Thalidomide in humans, while hydrolysates, the 5-hydoxylated metabolites and the 5'-hydroxylated metabolites have been observed. Also, CYP2C19 has been shown to be involved in the hydroxylation reaction of Thalidomide in humans.

3.2.A.3).(2) Optical transition

On the basis of the following findings obtained from studies on the (+)-(R)-form and the (-)-(S)-form of Thalidomide, the applicant does not consider it to make sense to administer only either of the enantiomers.

The (+)-(R)-form and the (-)-(S)-form of Thalidomide underwent chiral inversion in the presence of albumin.

Stereoselective metabolic reactions were observed in liver S9 fractions of rats and rabbits but not in liver S9 fraction of humans.

When Thalidomide (racemate) was orally administered to healthy adults, plasma concentrations over time of the (+)-(R)-form and the (-)-(S)-form changed in a similar manner. When either the (+)-(R)-form or the (-)-(S)-form alone was administered, chiral inversion occurred in the body.

3.2.A.4) Excretion

The applicant explained that the following findings were observed regarding the excretion of Thalidomide.

When radiolabeled Thalidomide was orally administered to mice, rats, rabbits, or monkeys, the radioactivity was excreted mainly in urine, but was also detected in the bile and the expired air of some animal species.

The unchanged drug excreted in the urine of rabbits and monkeys accounted for approximately 2.7% and 0.9%, respectively, of the total radioactivity excreted, with most of the excreted radioactivity being accounted for by metabolites of Thalidomide. It appears that the major route of elimination of the unchanged drug is extra-renal excretion.

In rabbits, excretion of Thalidomide in milk was confirmed, with the concentration in milk being higher than that in plasma.

3.2.A.5) Pharmacokinetic drug interactions

The following findings have been reported regarding pharmacokinetic interactions of Thalidomide.

Thalidomide did not affect the activity of human CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Repeated doses of Thalidomide in rats caused an increase in the hepatic CYP450 level, which suggested that this enzyme could be induced by Thalidomide in humans.

Thalidomide did not induce or inhibit P-gp, such that the applicant considers that there is no possibility of pharmacokinetic interactions mediated by P-gp.

3.2.B ***Outline of the review by the PMDA***

3.2.B.(1) Discussion on non-clinical PK of Thalidomide based on publications

In the present application, the PMDA did not evaluate the submitted data on non-clinical PK studies because the data were submitted for reference purposes.

The reasons for not submitting data on PK studies were given by the applicant as follows: There are many publications on Thalidomide, the active ingredient, including those containing study results necessary for application for marketing approval, and a judgment was made that these publications could be used as data supporting this application. Therefore, non-clinical PK studies necessary for applying for approval of a drug with new active ingredients could be omitted.

The PMDA considers as follows:
Although results of non-clinical PK studies have not been submitted as evaluation data in the present application, findings on the absorption, distribution, metabolism, excretion, and pharmacokinetic drug interactions are judged to generally be available from publications regarding the PK of Thalidomide. However, it is inappropriate that the applicant present a discussion based on a simple comparison of study results obtained under different conditions (for example, effects of solvents on the urinary excretion rate of radioactivity after the administration of Thalidomide samples labeled at different positions). Also, as discussed below [see 3.2.B.(2) Pharmacokinetic drug interactions"], it will be necessary to collect further non-clinical information on the possibility of interactions particularly with drugs that may be co-administered with Thalidomide in clinical practice, and based on any findings that may be obtained in the future, to assess whether or not additional investigation is necessary.

3.2.B.(2) Pharmacokinetic drug interactions

The PMDA asked the applicant to explain the findings currently available regarding the interactions of Thalidomide mediated by transporters other than P-gp.

The applicant responded as follows:
As regards the possible interaction with transporters other than P-gp, the following findings were obtained from a publication (*Eur J Drug Metab Pharmacokinet.* 2005;30:49-61) which suggests the involvement of both active transport (e.g. nucleoside transporters) and passive diffusion in the membrane permeability of Thalidomide.

- In a study using Caco-2 cells, the membrane permeability coefficient of Thalidomide (10 μmol/L) decreased with the addition of glutamic acid, cytidine, adenine, cyclophosphamide, or fluorouracil, as compared with the control group.

- The membrane permeability coefficient of Thalidomide (10 μmol/L) decreased with the addition of an ATP inhibitor, 2,4-dinitrophenol, or sodium azide, as well as when the Na concentration or pH was changed, as compared with the control group, but these effects disappeared when Thalidomide was administered at a concentration of 100 μmol/L.

The PMDA asked for the applicant's view on the necessity of advising caution about possible pharmacokinetic interactions between Thalidomide and CYP450 substrates, given that daily administration of Thalidomide caused an increase in CYP450 levels in the rat liver [see 3.2.A.5) Pharmacokinetic drug interactions"].

The applicant responded as follows:
Results of studies in rats suggested enzyme induction after multiple doses of Thalidomide in humans. However, it has been reported that when multiple 200 mg doses of Thalidomide were administered to healthy women for 21 days, there was no difference in PK parameter values of ethinylestradiol and norethisterone, compounds known to be metabolized by CYP3A4, before versus after Thalidomide administration [see "4.2 Clinical pharmacology data"], which suggests that Thalidomide does not induce CYP3A4 in humans. Also, there are no findings on the induction of CYP450 isoforms, nor are findings or cautions on enzyme induction described in the package inserts of the Thalidomide product approved in the US.

Based on the above, the applicant considers it unnecessary to advise caution about possible pharmacokinetic interactions due to enzyme induction by Thalidomide. If the applicant in future comes across new information that raises safety concerns regarding CYP450 isoforms, further investigation will be warranted.

The PMDA considers as follows:
Since it has been suggested that Thalidomide may affect the pharmacokinetics and pharmacodynamics of other drugs mediated by transporters (*J Pharmacol Exp Ther.* 2006;319:82-104), basic findings on Thalidomide such as its possible interactions with other drugs mediated by transporters other than P-gp may be useful for proper use of Thalidomide. Therefore, it is desirable that the applicant voluntarily conducts studies to assess such possibilities instead of simply collecting information from publications, academic reports, etc. In particular, since the applicant also recognizes the possibility of enzyme induction after multiple doses of Thalidomide, the applicant should conduct studies promptly to determine whether Thalidomide induces CYP450 isoforms and to provide the information obtained.

3.3 Toxicology data

3.3.A *Summary of the submitted data*

No evaluation data on the toxicology of Thalidomide has been submitted. Instead, the applicant discussed this topic using the data from publications. The study data was judged to be appropriate for assessing the safety of Thalidomide, by taking into account the clinical track record of the drug, although some data that does not satisfy the Japanese guidelines was included.

3.3.A.(1) Single-dose toxicity

Data from single-dose toxicity studies in mice, rats, and dogs has been submitted. The LD_{50} in mice was not less than 5000 mg/kg by oral and by subcutaneous administration, while the LD_{50} by intraperitoneal administration has variously been reported to be not less than 5000 mg/kg and not less than 10,000 mg/kg. The LD_{50} in rats was reported to be not less than 8000 mg/kg by oral administration and not less than 6000 mg/kg by intraperitoneal administration. The minimal lethal dose in dogs was reported to be not less than 1538 mg/kg by oral administration. Thus, the lethal dose of Thalidomide is high regardless of animal species and of the administration route tested, from which the acute toxicity of Thalidomide is judged to be low.

3.3.A.(2) Repeated-dose toxicity

Data from repeated-dose toxicity studies in mice, rats, and dogs has been submitted. No Thalidomide-related deaths occurred in any of the studies.

Data from a 13-week oral administration study (0, 30, 300, 3000 mg/kg/day) in mice is presented. A low lymphocyte count was observed in male animals receiving not less than 300 mg/kg/day (a significantly reduced level in the 300 mg/kg/day group, a tendency toward a reduced level in the 3000 mg/kg/day group), and low white blood cell and lymphocyte counts were observed in female animals receiving 3000 mg/kg/day. Urinalysis showed orange-pink colored urine, which was

attributed to degradation products of Thalidomide. High liver weight and centrilobular hepatocytic hypertrophy, both possibly related to enzyme induction, were observed. The no observed adverse effect level (NOAEL) is considered to be 30 mg/kg/day in males and 300 mg/kg/day in females.

Data from a 13-week oral administration study (0, 30, 300, 3000 mg/kg/day) in rats is presented. Reduced body weight gain was observed in both males and females of all Thalidomide groups. In males, decreased food consumption was also observed, and the extent of the reduction in body weight gain was more marked than in females. As regards the endocrine system, low levels of thyroid hormones (T3 and T4) were observed in both males and females (only in females in the 30 mg/kg/day group). High testis weight (in all Thalidomide groups) and high liver weight (in males and females of the 3000 mg/kg/day group) were observed, but no abnormal findings were observed in the testis or the liver histopathologically. Neurobehavioral examination revealed decreased grip strength of the anterior limbs only in male animals. Since this finding is suggested to be related to the reduction in body weight gain, and no abnormalities were observed in other evaluation parameters or in histopathological examination of nerves, peripheral neuropathy is considered to not be induced by Thalidomide in rats. The NOAEL is considered to be 30 mg/kg in males and less than 30 mg/kg in females.

Data from a 53-week oral administration study (0, 43, 200, 1000 mg/kg/day; recovery period, 5 weeks) in dogs is presented. Hematology and biochemical tests showed changes in several parameters, whereas no histological changes were observed in related organs and the parameter values normalized after the washout period of 5 weeks, which suggested that the observed changes were of minimal toxicological significance. As changes related to Thalidomide administration, yellow-green discoloration of the femur, ribs, etc., green-colored urine, and white substances in feces (inferred to be unabsorbed Thalidomide) were observed. In female animals in Thalidomide groups, prolongation of estrus cycle and mammary hypertrophy were observed, and histopathological examination showed dilatation of the glandular cavity and mammary epithelial hyperplasia. In males of the high dose groups, pigmentation of the biliary canaliculus with bile was observed. As regards the endocrine system, no changes were observed in TSH or T3 levels, whereas T4 was dose-dependently decreased. No particular changes were observed in the nervous system. Most of these changes reverted to normal after washout, though green-colored urine, bone discoloration, and mammary changes persisted even after the washout period of 5 weeks. The NOAEL is considered to be less than 43 mg/kg in female animals and 200 mg/kg/day in male animals. However, since no detailed data on the low T4 levels was presented in the publication reporting the study results [Note by PMDA: “T4 level in 1000 mg/kg/day group was low, being 34.8% of the level observed in the control group” was the only description given], the possibility cannot be excluded that the NOAEL is lower than 200 mg/kg/day in this regard in male animals.

3.3.A.(3) Genotoxicity

Genotoxicity data presented is that of a bacterial reverse mutation assay, a chromosomal aberration assay using cultured mammalian cells, and a mouse micronucleus test. All of these tests produced negative results.

3.3.A.(4) Carcinogenicity

Data from 2 carcinogenicity studies, one employing subcutaneous administration once weekly for 57 weeks in mice (15 mg/mouse) and the other employing subcutaneous administration once daily for 220 days in mice (7.5 mg/mouse), is presented. Although sarcoma formation was observed at the injection site in 2 of 20 animals in the 57-week study and in 1 of 3 animals in the 220-day study, the carcinogenicity of Thalidomide is considered to be low. In the US package insert of a Thalidomide preparation with a formulation different from that of the proposed product, it is stated that, in 2-year carcinogenicity studies in mice and rats, no Thalidomide-related tumorigenic effects were observed in male or female mice in the 3000 mg/kg/day group, female rats in the 3000 mg/kg/day group, or male rats in the 300 mg/kg/day group.

3.3.A.(5) Reproductive and developmental toxicity

Data on reproductive and developmental toxicity in mice, rats, rabbits, and monkeys is presented. Fetal toxicity (embryonic lethality, teratogenicity) of Thalidomide is shown, although results vary depending on animal species and study design. Also, Thalidomide is shown to be excreted into milk.

It is well known that Thalidomide is teratogenic in humans. Thalidomide is therefore contraindicated in pregnant or possibly pregnant women, and it is essential that women with child-bearing potential take strict contraceptive measures together with their partners. Since Thalidomide is reported to be excreted into milk and seminal fluid, lactating women must stop breast-feeding and male patients must take strict contraceptive measures (use of a condom is essential even in vasectomized men). These points will be described in the package insert, advising sufficient caution.

3.3.A.(6) Other toxicity studies

In order to clarify the neurotoxicity of Thalidomide, studies in rabbits and dogs have been conducted. A 33-week oral administration study (0, 100 mg/kg/day) was conducted in rabbits, which showed a decrease in the conduction velocity and a decrease in the thickness of the myelin sheath in the sural nerve. A 53-week oral administration study (0, 43, 200, 1000 mg/kg/day) was conducted in dogs, which showed no peripheral neuropathy. These results suggest that there are species differences in the occurrence of neuropathy caused by Thalidomide.

3.3.B *Outline of the review by the PMDA*

In the present application, the PMDA did not evaluate the submitted data on non-clinical toxicity studies because the data were submitted for reference purposes.

The PMDA noted that the applicant did not take a sufficiently serious view of the effect of Thalidomide on thyroid function in reference data submitted for the present application. In the clinical use of Thalidomide in foreign countries, cases showing a suspected relationship with hypothyroidism have also been reported (*Am J Med.* 2002;112:412-413). Therefore, the PMDA asked the applicant to reassess the relationship between Thalidomide administration and hypothyroidism and to discuss the necessity of providing relevant information in the package insert, etc.

The applicant responded as follows:
The low T4 levels observed in rats and dogs were probably caused by Thalidomide. Hypothyroidism will be included in the adverse reactions to Thalidomide and described as such in the Japanese package insert by referring to the reports from foreign studies.

The PMDA accepted the applicant's response.

The PMDA considers that caution should be exercised regarding the known teratogenicity, neurotoxicity, gastrointestinal toxicity, dermal toxicity, and white blood cell count decreased in the clinical use of Thalidomide. Also, since low T4 levels, mammary changes, etc., have been observed, adequate attention should be paid to hypothyroidism and effects on other endocrine systems.

4. Clinical data

4.1 Biopharmaceutical data

4.1.A *Summary of the submitted data*

The bioavailability (BA) of Thalidomide and effects of food on the PK of the proposed product have not been investigated. Instead, the following publications on the biopharmaceutical findings

on Thalidomide products marketed in foreign countries were submitted as reference data.

4.1.A.1) Publications on the biopharmaceutical findings on the products marketed in foreign countries

In a crossover study that investigated the bioequivalence (BE) between Thalidomide capsules marketed by Celgene Corporation and Thalidomide capsules marketed by Tortuga in Brazil in healthy adults, the BE of the 2 products was not demonstrated for C_{max}, whereas their $AUC_{0-\infty}$ were comparable (*J Clin Pharmacol.* 1999;39:1162-1168).

In a crossover study in healthy adults that compared (a) relative BA between Thalidomide capsules of Celgene Corporation and Thalidomide tablets of Serral S.A. de C.V. in Mexico, and (b) the effect of food on the PK of Celgene Thalidomide capsules (*Biopharm Drug Dispos.* 2000;21:33-40), the Celgene capsules showed lower T_{max} and $t_{1/2}$ than the Serral tablets, and C_{max} was approximately double, and $AUC_{0-\infty}$ approximately 10% greater, than those of the Serral tablets. When the Celgene capsules were administered along with a high-fat meal, T_{max} increased by 2 hours as compared with that observed under fasting conditions, while the effect of a high-fat meal on C_{max} and $AUC_{0-\infty}$ was small.

4.1.B *Outline of the review by the PMDA*

In the present application, the PMDA did not evaluate the submitted data on biopharmaceutics because the data were submitted for reference purposes.

4.1.B.1) Effects of food on PK of Thalidomide

Effects of food on the PK of the proposed product have not been investigated. Instead, the effects were inferred based on the results of studies conducted using Thalidomide products that are marketed in foreign countries in formulations different from that of the proposed product.

In a Japanese clinical study [see "4.2 Clinical pharmacology data"] in which the PK of Thalidomide was evaluated, the interval between the start of a meal and the administration of Thalidomide was approximately 60 (12 of 13 patients) to 90 (1 of 13 patients) minutes. The PK data in the Japanese clinical study was that obtained by administration after a meal.

The PMDA asked for the applicant's view on the necessity of investigating the effects of food on the PK of the proposed product.

The applicant responded as follows:

Judging from the publication (*Biopharm Drug Dispos.* 2000;21:33-40), the extent of Thalidomide absorption with the Celgene capsules appears to be minimally affected by a high-fat meal. Also, the proposed product and Thalidomide 100 mg capsules of Penn Pharmaceutical Services Ltd. of the UK showed a similar rate and pattern of dissolution [see 4.1.B.2) Comparison of the results of dissolution tests between the proposed product and the Thalidomide products marketed in foreign countries"]. Moreover, in the Japanese clinical study (Study FPF300-02-01), the mean C_{max} and $AUC_{0-\infty}$ after oral administration of 100 mg of Thalidomide were similar when adjustments were made for body weight to those obtained in non-Japanese HIV patients after oral administration of the same dose of the Celgene capsules (*AIDS Res Hum Retroviruses.* 1999;15:1047-1052) [see "4.2 Clinical pharmacology data"].

These results infer that the proposed product shows a behavior similar to that of the Celgene capsules and that food therefore does not affect the PK of the proposed product, as was the case with the Celgene capsules. Therefore, it was judged unnecessary to investigate the effects of food on the PK of the proposed product.

The PMDA considers as follows:

The objective of evaluating the effects of food on the PK of the proposed product (the product to be marketed) is to investigate the effects of food on the PK of Thalidomide, including the processes of disintegration and dissolution of the proposed product, following administration of the proposed product. Since the response of the applicant is based on a discussion of the study results for biopharmaceutics of other Thalidomide products with different formulations, it is difficult to evaluate and compare the effects of food on the PK of the proposed product, which therefore remain unclear.

Since the relationship between the PK of Thalidomide versus the efficacy and safety of the drug is currently unclear [see "4.2 Clinical pharmacology data"], it will be necessary to advise extra caution to avoid the possible effects of food on the PK of Thalidomide whenever possible, by complying with administration before bedtime, the dosage regimen used in clinical studies, and by dividing the interval between meals and administration to the extent practiced in the Japanese clinical study. It will be necessary to take measures to minimize the effects of food on the PK of Thalidomide by thoroughly advising the above caution on the dosage regimen, and to evaluate the effects of food at least during the early phase after marketing, thereby appropriately providing such information.

Deliberation should be made at the Expert Discussion regarding the conduct of post-marketing clinical studies on the effects of food on the PK of Thalidomide.

4.1.B.2) Comparison of the results of dissolution tests between the proposed product and the Thalidomide products marketed in foreign countries

The PMDA asked the applicant to explain the results of studies on the dissolution of Thalidomide which were presented at academic society meetings by investigators from the Department of Pharmacy, Gunma University Hospital, etc.

The applicant responded as follows:
Results of studies on the dissolution of Thalidomide, which were commissioned by the applicant, were presented at academic society meetings, as follows:

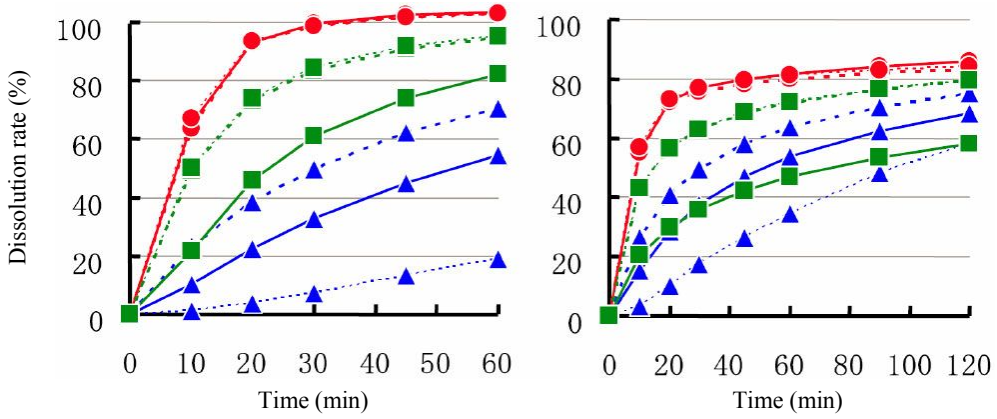
- The dissolution profiles of thalidomide formulations made in Japan and Mexico
  (Fujita, et al., the 127th Annual Meeting of the Pharmaceutical Society of Japan, March 2007, in Toyama)

- Study on the relationship between the dissolution and time-course changes in blood concentration: comparison between Thalidomide preparations manufactured in Japan and foreign countries
  (Fujita, et al., the 17th Annual Meeting of the Japanese Society of Pharmaceutical Health Care and Sciences, September 2007, in Gunma)

The dissolution of the proposed product and the Thalidomide products marketed in foreign countries (Thalidomide 100 mg capsules of Penn Pharmaceutical Services Ltd., Thalidomide 100 mg tablets of Serral S.A. de C.V.) was investigated according to Method 2 of the US Pharmacopeia (USP) and to the dissolution test method developed by the applicant (puddle method, 75 rpm, 900 mL of the 1st fluid for the dissolution test using polysorbate 80 [■■■■], at 37°C). The proposed product (figure below, ■ 3 lots) and the Penn Thalidomide 100 mg capsules (figure below, ● 3 lots) showed similar dissolution profiles. Thus, the proposed product and the Penn Thalidomide 100 mg capsules yielded "similar" results for each of the test methods performed, as judged by the f_2 function stipulated by "Guidelines for Bioequivalence Testing of Generic Drugs," except 1 lot of the Penn Thalidomide 100 mg capsules that showed a large lot-to-lot variation. In contrast, the Serral Thalidomide 100 mg tablets (figure below, ▲ 3 lots) showed lower dissolution than the proposed product, and was judged to be "not similar" to

the proposed product by each test method performed (see figure below).

Time-course change in the dissolution rate of each Thalidomide preparation (left, Method 2 of the USP; right, dissolution test method developed by the applicant)



(Each lot was tested 6 times)

On the basis of the results of the above studies, the applicant considers that the dissolution of the proposed product is similar to that of the Penn Thalidomide 100 mg capsules and that the proposed product is expected to exhibit clinical efficacy.

4.1.B.3) Switching from the Thalidomide products marketed in foreign countries to the proposed product

Results of the dissolution tests of the proposed product and the Thalidomide products marketed in foreign countries have shown that the dissolution of the proposed product is different from those of some products marketed in foreign countries [see 4.1.B.2) Comparison of the results of dissolution tests between the proposed product and the Thalidomide products marketed in foreign countries"].

The PMDA asked the applicant to explain matters to which attention should be paid in switching from the products marketed in foreign countries to the proposed product from a biopharmaceutical viewpoint.

The applicant responded as follows:

After application of the proposed product for approval, 2 reports were published on the biopharmaceutical findings of the proposed product and the products marketed in foreign countries [see 4.1.B.2) Comparison of the results of dissolution tests between the proposed product and the Thalidomide products marketed in foreign countries"]. In these reports, dissolution tests were performed on the proposed product and on the Thalidomide products marketed in foreign countries, and plasma Thalidomide concentrations over time following administration of each product were compared based on the publications (Japanese clinical study [Study FPF300-02-01] [see "4.2 Clinical pharmacology data"], *Biol Pharm Bull.* 2006;29:2331-2334, *Biopharm Drug Dispos.* 2000;21:33-40). As a result, the following conclusions have been reached.

- The Mexican product and the proposed product show different blood Thalidomide concentrations over time due to the difference in dissolution.

- In switching from the privately-imported Mexican product to the proposed product, it is necessary to pay attention to the differences in the blood concentration over time ([a] increase in C_{max}, [b] decrease in T_{max}, [c] decrease in apparent $t_{1/2}$, [d] decrease in trough

value) as well as the occurrence of accompanying adverse drug reactions.

The PMDA considers as follows:
The dissolution tests have shown the dissolution of the proposed product to be better than that of the tested products marketed in foreign countries [see 4.1.B.2) Comparison of the results of dissolution tests between the proposed product and the Thalidomide products marketed in foreign countries"]. Since the published data on the products marketed in foreign countries and the data from the Japanese clinical study (Study FPF300-02-01) were both obtained in human subjects but under different conditions aside from formulation, it is difficult to make direct comparisons of these products. Nevertheless, the results have shown that C_{max} and $AUC_{0-\infty}$ following administration of 100 mg of Thalidomide tended to be higher in the Japanese clinical study than in foreign clinical studies [see "4.2 Clinical pharmacology data"]. Therefore, patients may have relatively greater exposure to Thalidomide when the privately-imported foreign-marketed product is switched to the proposed product. Thus, it will be necessary to advise caution in monitoring the patient's conditions very carefully immediately after switching products.

4.2 Clinical pharmacology data

4.2.A *Summary of the submitted data*

The PK of Thalidomide in humans was investigated in a Japanese clinical study involving patients with multiple myeloma.

4.2.A.1) Japanese clinical study (Study FPF300-02-01)

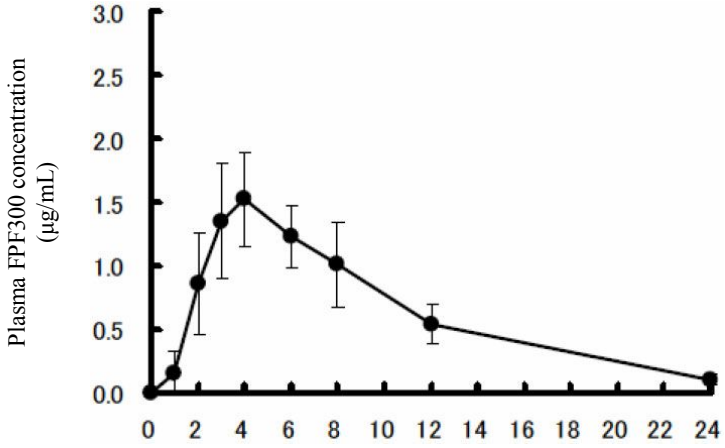
One hundred milligrams of Thalidomide was orally administered to 37 subjects with relapsed or chemotherapy-resistant multiple myeloma (13 of them for PK analysis) once daily before bedtime (after breakfast at the initial administration in subjects for PK analysis), and the plasma Thalidomide concentration was measured after the initial administration. The plasma Thalidomide concentration reached C_{max} at 4 hours after administration, after which it decreased gradually, falling to a level of one-sixteenth C_{max} at 24 hours after administration. PK parameter values of plasma Thalidomide concentrations are shown in the table below.

PK parameter values following initial administration of 100 mg of Thalidomide

C_{max} (μg/mL)	T_{max}* (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg·h/mL)
1.68 ± 0.411	4 (3-8)	4.86 ± 0.437	15.9 ± 3.05

Mean ± SD (13 subjects); *, Median (range)

Plasma Thalidomide concentrations over time
following initial administration of 100 mg of Thalidomide



4.2.A.2) Findings on the PK of Thalidomide in humans

4.2.A.2).(1) Single oral dose

(*J Clin Pharmacol.* 2001;41:662-667, *AIDS Res Hum Retroviruses.* 1999;15:1047-1052)

A crossover study was conducted in which 50, 200, and 400 mg Celgene capsules were orally administered in a single dose to healthy non-Japanese adults. C_{max} increased less than proportionally to the dose, whereas $AUC_{0-\infty}$ increased in a dose-dependent manner. T_{max} increased as the dose increased, while CL/F showed little difference among the 3 doses. $t_{1/2}$ was 5.5 hours at 50 and 200 mg, but increased to 7.3 hours at 400 mg.

A crossover study was conducted in which 100 and 200 mg Celgene capsules were orally administered in a single dose to non-Japanese patients with HIV infection. $AUC_{0-\infty}$ increased in a dose-dependent manner, the same result as that obtained in another report (*Antimicrob Agents Chemother.* 1997;41:2797-2799). The dose-adjusted mean C_{max} was lower after 200 mg than after 100 mg administration. No difference was observed in the PK of Thalidomide between smokers and non-smokers.

4.2.A.2).(2) Multiple oral doses

(*J Clin Oncol.* 2000;18:708-715, *J Pharm Sci.* 1999;88:121-125, *Clin Pharmacol Ther.* 1998;64:597-602)

Thalidomide was orally administered in multiple doses once daily to non-Japanese patients with prostate cancer. Patients in the low-dose group were administered 200 mg; patients in the high-dose group were initially administered 800 mg and then 200 mg, followed by a 200 mg increase every 2 weeks up to 1200 mg. $t_{1/2}$ following multiple doses was 7.08 ± 1.87 hours in the low-dose and 16.19 ± 9.57 hours in the high-dose group (mean value obtained by administering 200 to 1200 mg), a higher value was obtained in the high-dose group. The steady-state C_{max} increased in a dose-dependent manner within the 200 to 1200 mg dose range, while CL/F was not dose-dependent. Neither CL/F nor $t_{1/2}$ showed age-related differences.

Thalidomide was administered once daily to non-Japanese patients with glioma starting from 800 mg, followed by a 200 mg increase every 2 weeks up to 1200 mg. CL/F, Vd/F, and $t_{1/2}$ (mean value obtained by administration of 800 to 1200 mg) were 12.65 ± 6.63 L/h, 123.75 ± 72.90 L, and 8.31 ± 7.12 hours, respectively. There was a negative correlation between age and CL/F.

Andrulis 200 mg capsules were orally administered in multiple doses once daily for 21 days to healthy non-Japanese women. Little difference was observed in C_{max}, $AUC_{0-\infty}$, $t_{1/2}$, and CL/F between the day of the first administration and Day 21.

4.2.A.2).(3) Distribution

(*J Chromatogr B Analyt Technol Biomed Life Sci.* 2002;767:145-151)

When 100 mg of Thalidomide was orally administered in multiple doses once daily for 8 weeks to non-Japanese patients with HIV infection, the unchanged drug was detected in the plasma and seminal fluid at Weeks 4 and 8 after the start of administration.

4.2.A.2).(4) Metabolism

(*Br J Pharmacol Chemother.* 1965;25:324-337, *Clin Cancer Res.* 2003;9:1680-1688, *J Pharm Pharmacol.* 1998;50:1409-1416, *J Biochem Mol Toxicol.* 2000;14:140-147, *Cancer Biol Ther.* 2002;1:669-673, *Clin Cancer Res.* 2004;10:5949-5956, *J Pharmacol Exp Ther.* 2004;310:571-577)

Twelve different types of hydrolysates are reportedly produced by non-enzymatic hydrolysis of Thalidomide.

In an *in vitro* study using human liver microsomes or the liver S9 fraction, 5-hydroxylated and 5'-hydroxylated metabolites were detected in addition to the hydrolysates, but both hydroxylated metabolites were produced only in minimal amounts and the P450 isoform involved in production of the hydroxylated metabolites was CYP2C19, according to the report.

When Thalidomide was orally administered to healthy non-Japanese adults, patients with Hansen's disease, multiple myeloma, or prostate cancer, 3 different types of hydrolysates (4-phthalimide glutaric acid monoamide, 2-phthalimide glutaric acid monoamide, α-(o-carboxybenzamide) glutarimide), the 5-hydroxylated metabolite, and the 5'-hydroxylated metabolite were detected in the plasma and urine.

4.2.A.2).(5) Urinary excretion

(*Clin Cancer Res.* 2004;10:5949-5956, *Drug Metab Dispos.* 1989;17:402-405)

When 200 mg of Thalidomide was administered orally in a single dose to non-Japanese patients with multiple myeloma, the urinary excretion rate of the unchanged drug by 24 hours after administration was less than 1%.

When Champion 200 mg tablets were orally administered in a single dose to healthy non-Japanese adult men, the urinary excretion rate of the unchanged drug by 24 hours after administration was 0.6%, and renal clearance was 0.08 ± 0.03 L/h. The urinary excretion rate of the unchanged drug from patients with multiple myeloma treated in a similar manner was 0.9%. Renal excretion of Thalidomide is reportedly low, with the major route of elimination being extra-renal.

4.2.A.2).(6) Pharmacokinetic drug interactions (*Clin Pharmacol Ther.* 1998;64:597-602)

Andrulis 200 mg capsules were orally administered in multiple doses once daily for 21 days to healthy non-Japanese women to measure PK parameters of Thalidomide and to assess the effects of the drug on PK of oral contraceptives (ethinylestradiol, norethisterone). Little difference was observed in the C_{max}, $AUC_{0-\infty}$, $t_{1/2}$, or CL/F of Thalidomide between the first day of administration and Day 21. Neither were effects of Thalidomide observed on C_{max}, $AUC_{0-\infty}$, $t_{1/2}$, or CL/F of ethinylestradiol or norethisterone.

4.2.A.2).(7) Enantiomers (*Chirality.* 1995;7:44-52)

When 1.0 mg/kg of the (+)-(R)-form or the (-)-(S)-form or 1.5 mg/kg of the racemate of Thalidomide was orally administered in a single dose to healthy non-Japanese men, chiral inversion was confirmed in the blood. The rate of chiral inversion of the R-form was more rapid

than that of the S-form, and the S-form was eliminated more rapidly than the R-form. After administration of racemates, the ratio of $AUC_{0-\infty}$ of the R-form to that of the S-form was 1.60 ± 0.12. Since Thalidomide reportedly undergoes rapid chiral inversion *in vivo*, there is little difference in pharmacological action between the enantiomers.

4.2.A.2).(8) PK in patients on hemodialysis (*J Pharm Pharmacol.* 2003;55:1701-1706)

When Celgene 200 mg capsules were orally administered in multiple doses once daily for 5 days to non-Japanese patients with advanced renal disease, CL/F doubled during hemodialysis as compared with the inter-dialytic interval value. However, reportedly, no dose adjustment is required in patients on hemodialysis, as judged from calculating the supplementary dose required during hemodialysis 10 to 15 hours after administration of the Thalidomide.

4.2.A.2).(9) Applicant's discussion on factors possibly affecting the PK of Thalidomide

a. Gender

In the Japanese clinical study (Study FPF300-02-01), weight-adjusted mean C_{max} and $AUC_{0-\infty}$ (see table below) were 6.1% and 10% higher in women than in men, respectively, but these differences were within the inter-individual variation ranges, according to the applicant.

	No. of subjects	Mean body weight (kg)	C_{max} (μg/mL)		$AUC_{0-\infty}$ (μg·h/mL)	
			Observed value	Weight-adjusted value*	Observed value	Weight-adjusted value*
Men	5	63	1.54 ± 0.43	1.58 ± 0.37	14.30 ± 2.41	14.67 ± 1.35
Women	8	59	1.76 ± 0.41	1.68 ± 0.27	16.85 ± 3.11	16.20 ± 2.47

Mean ± SE; *, value adjusted to body weight of 60 kg

In a publication (*Biopharm Drug Dispos.* 2000;21:33-40), the slightly greater values of C_{max} and $AUC_{0-\infty}$ in women than in men are reportedly explainable by the difference in body weight (22%). In both the Japanese clinical study and the publication, there was little difference in T_{max} and $t_{1/2}$ between men and women. Thus, the applicant considers that there is no difference in the PK of Thalidomide between genders.

b. Age

In a publication (*J Clin Oncol.* 2000;18:708-715) in which Thalidomide was administered in multiple doses to patients with glioma (28 to 72 years old), a negative correlation was observed between age and CL/F. In contrast, in a publication (*J Pharm Sci.* 1999;88:121-125) on patients with prostate cancer (55 to 80 years old), there was no correlation between CL/F or $t_{1/2}$ and age.

Thus, the applicant explained that effects of age on the PK of Thalidomide could not be evaluated.

4.2.B *Outline of the review by the PMDA*

4.2.B.1) PK of Thalidomide at doses other than 100 mg and following multiple doses

In the proposed dosage and administration, it is stated that Thalidomide can be administered daily at a dose of up to 400 mg/day. However, no investigation has been performed on the PK of the proposed product at doses other than 100 mg or following multiple doses.

The PMDA asked for the applicant's view on the necessity of evaluating PK at doses other than 100 mg or following multiple doses.

The applicant responded as follows:

a. On the necessity of evaluating PK at doses other than 100 mg

When C_{max} and $AUC_{0-\infty}$ obtained in the Japanese clinical study (Study FPF300-02-01) were

adjusted for body weight and compared with those of the publication (*AIDS Res Hum Retroviruses.* 1999;15:1047-1052) about the study using Celgene capsules, it was found that the values were comparable (see table below).

	No. of subjects (men/women)	Mean body weight (kg)	C_{max} (μg/mL)	$AUC_{0-\infty}$ (μg·h/mL)
Japanese clinical study	13 (5/8)	60	1.68 ± 0.41	15.9 ± 3.0
		77	1.28 ± 0.23	12.2 ± 1.7
AIDS Res Hum Retroviruses. 1999;15:1047-1052	14 (14/0)	77*	1.15 ± 0.24	9.8 ± 1.6

Mean ± SD; *, PK parameter values were obtained from 14 subjects, but body weight is expressed as the mean of all 16 enrolled subjects.

In the publication on the study using Celgene capsules, C_{max} and $AUC_{0-\infty}$ tended to increase dose-dependently within the 50 to 400 mg dose range [see 4.2.A.2).(1) Single oral dose"].

Based on the above, it was judged that PK parameter values (dose-dependency) of the proposed product at doses other than 100 mg could be estimated from the data in the publications.

b. On the necessity of evaluating PK following multiple doses

The applicant explained as follows: As judged by the PK parameter values following multiple doses of Thalidomide, the drug does not accumulate in the body after multiple doses, and blood Thalidomide concentrations over time show a dose-dependent steady-state increase in C_{max} and dose-independent changes in the CL/F level [see 4.2.A.2).(2) Multiple oral doses"]. From these results, it can be inferred that the proposed product shows similar tendencies in PK parameter values, requiring no additional studies.

The PMDA asked the applicant to discuss Thalidomide accumulation following multiple doses based on PK parameter values following a single dose of the proposed product.

The applicant responded as follows:

In the Japanese clinical study (Study FPF300-02-01), the accumulation factor (mean ± SD [standard deviation]) calculated from the elimination rate constant (Kel) of Thalidomide following a single dose and the dosing interval was 1.034 ± 0.012. In the publication (*AIDS Res Hum Retroviruses.* 1999;15:1047-1052), the mean accumulation factor calculated from PK parameter values following a single dose was 1.029. Also, although no observed values of AUC_{0-24} following multiple doses are described in any publications, 1 article (*Clin Pharmacol Ther.* 1998;64:597-602) noted that no accumulation of Thalidomide in the body was seen after multiple doses.

Based on the above, it is anticipated that accumulation of the proposed product following multiple doses is similar to that of other Thalidomide products and therefore that the proposed product does not accumulate in the body.

Regarding the necessity of evaluating PK at doses other than 100 mg or following multiple doses, using the proposed product, the PMDA considers as follows:

No information is available on such matters as the effects of formulation differences among Thalidomide products used in the Japanese clinical study and those in the publications, or on the effects of differences in patient backgrounds between these studies. Neither is there any rational explanation given for judging that the findings obtained from other Thalidomide products can be used. Therefore, it is difficult to accurately assess the PK of the proposed product based on the findings reported in publications on other Thalidomide products.

Meanwhile, given that the appropriateness of a dose increase is supposed to be comprehensively determined in clinical practice based on the clinical efficacy and safety in individual patients, that no accumulation of Thalidomide is expected after multiple doses as estimated from PK data following a single dose of 100 mg of the proposed product, and that various Thalidomide products marketed in foreign countries are currently imported individually for personal use, it is considered appropriate, instead of withholding approval until further studies are conducted on the PK of the proposed product at doses other than 100 mg and following multiple doses, to collect, as soon as possible after marketing, data on (a) PK at doses other than 100 mg, and (b) PK following multiple doses, and to provide the information obtained to medical professionals in an appropriate manner.

Deliberation should be made at the Expert Discussion on the conduct of PK studies of Thalidomide in post-marketing clinical studies, etc.

4.2.B.2) Factors affecting the PK of Thalidomide

The PMDA asked the applicant to discuss factors possibly affecting the PK of Thalidomide.

The applicant responded as follows:

As judged from data on pharmacokinetics, biopharmaceutics, and clinical pharmacology, it is unlikely that food, gender, or P-gp affects the PK of Thalidomide. Effects of age on the PK of Thalidomide could not be assessed [see 4.2.A.2) Findings on the PK of Thalidomide in humans"]. As a result of the following investigation on other factors, it was concluded that body weight was the only factor affecting the PK of Thalidomide.

a. Body weight

In the Japanese clinical study (Study FPF300-02-01), a negative correlation was observed between C_{max} or $AUC_{0-\infty}$ and body weight (C_{max}, r = -0.620, P = 0.024; $AUC_{0-\infty}$, r = -0.661, P = 0.014). Thus, body weight appears to affect the PK of Thalidomide.

b. CYP450

In addition to non-enzymatic hydrolysis under physiological pH, Thalidomide reportedly undergoes metabolism by CYP2C19 to form hydroxylated metabolites, but to a smaller extent than hydrolysates [see 4.2.A.2) Findings on the PK of Thalidomide in humans"]. Also, there are published clinical studies, one of which claimed to have confirmed the formation of hydroxylated metabolites while the other did not detect such metabolites. From these results, it is considered that, although Thalidomide is metabolized to a slight extent in the liver, CYP450 does not affect the PK of the drug because non-enzymatic hydrolysis is the major elimination pathway.

c. Renal function

Since the major elimination pathway of Thalidomide appears to be extra-renal [see 4.2.A.2) Findings on the PK of Thalidomide in humans"], renal function is considered not to affect the PK of Thalidomide.

The PMDA considers as follows:

Factors other than body weight have not necessarily been analyzed in sufficient detail. In addition, there is inconsistency in the data among publications, leaving ambiguity regarding factors affecting the PK of Thalidomide. It will be necessary to advise caution as to this possibility, at the current level of understanding, of body weight affecting the PK of Thalidomide, to continuously collect information from publications, etc. on factors possibly affecting the PK of Thalidomide, and thereby to provide information in an appropriate manner.

4.2.B.3) Relationships between extent of exposure and efficacy and safety

The PMDA asked the applicant to discuss the relationships between PK parameters and the

efficacy and safety of Thalidomide.

The applicant responded as follows:

a. Efficacy
In the Japanese clinical study (Study FPF300-02-01), no correlation was observed between C_{max} or $AUC_{0-\infty}$ and the percent changes in M protein level at Week 2 (first time point for assessing the "level of response") (C_{max}, $r = 0.26678$ [$P = 0.4019$]; $AUC_{0-\infty}$, $r = 0.17749$ [$P = 0.5811$]). Since the PK parameter values were obtained after the first administration, while efficacy was evaluated 2 weeks after starting administration, it is difficult to assess the relationship between the PK parameter values of Thalidomide and efficacy.

b. Safety
Adverse drug reactions observed in not less than 3 of 13 subjects who were evaluated for PK in the Japanese clinical study (Study FPF300-02-01) were constipation, neutrophil count decreased, sleepiness, dry mouth, white blood cell count decreased, dysgeusia, eruption, fatigue, urinary protein positive, monocyte count increased, numbness of lips, CRP increased, queasy, oedema, basophil count increased, tremor, and D dimer increased. Between-group comparisons by the Student *t* test of C_{max} and $AUC_{0-\infty}$ in subjects with each adverse drug reaction and in those without such reactions showed significant differences in C_{max} ($P = 0.0016$) and $AUC_{0-\infty}$ ($P = 0.0386$) for sleepiness and in C_{max} ($P = 0.0306$) for tremor, with C_{max} and $AUC_{0-\infty}$ values being higher in subjects with than in those without adverse drug reactions. No significant difference was observed in C_{max} or $AUC_{0-\infty}$ for other symptoms.

In 8 subjects who experienced sleepiness, this symptom occurred on the first day of treatment in 3, 2 days after starting treatment in 2, 8 days after in 2, and 15 days after in 1. Thus, symptoms occurred relatively soon after starting treatment, suggesting relationships with PK parameter values after the first administration. In contrast, in 3 subjects who experienced tremor, it occurred 22 days (100 mg), 29 days (100 mg), and 43 days (200 mg), respectively, after starting treatment, suggesting that the relationship between this symptom and PK parameter values after the first administration is not assessable.

The PMDA considers as follows:
Since the PK of Thalidomide was investigated only at limited doses, relationships between the extent of exposure to Thalidomide and efficacy and safety have not been fully evaluated, and thus remain unclear. The applicant's explanation appeared to partly contradict the discussion on drug accumulation.

4.2.B.4) Pharmacokinetic drug interactions
The PMDA asked for the applicant's view, based on the most recent findings, on pharmacokinetic interactions with drugs expected to be administered in combination with Thalidomide.

The applicant responded as follows:
No findings are available on the pharmacokinetic interactions between Thalidomide and the following drugs: cyclophosphamide, interferon, bortezomib, melphalan, prednisolone, vincristine sulfate, doxorubicin hydrochloride, dexamethasone phosphate, and zoledronic acid hydrate.

The PMDA has confirmed that pharmacokinetic interactions of Thalidomide with the above drugs that might be administered in combination with Thalidomide are not described in the package inserts of other Thalidomide products approved in the US and the EU. The PMDA has also confirmed that, similarly to the package inserts of dexamethasone, dexamethasone phosphate, and zoledronic acid hydrate that are approved in Japan, the package insert of the proposed product contains cautions about possible interactions of Thalidomide with dexamethasone, dexamethasone

phosphate, and zoledronic acid hydrate.

The PMDA recommends that findings on the mechanisms of interactions with Thalidomide be continuously collected and investigated. The PMDA also considers that future studies on combination of Thalidomide with other anti-neoplastic agents, if conducted, be designed to assess pharmacokinetic interactions between Thalidomide and these other anti-neoplastic agents.

4.3 Data on clinical efficacy and safety

4.3.A *Summary of the submitted data*

Data from a Japanese clinical study was submitted as evaluation data related to the clinical efficacy and safety of Thalidomide.

4.3.A.1) Japanese clinical study (Study Number, FPF300-02-01; Publication, None; Study Period, [redacted] 20[redacted] to [redacted] 20[redacted])

A multi-center, open-label, dose escalation study was conducted at 22 study sites in Japan to evaluate the efficacy and safety of Thalidomide in patients (target number of patients, 35) with multiple myeloma (MM) relapsing after hematopoietic stem cell transplantation or with chemotherapy-resistant MM (primary cases treated with not more than 3 regimens, including steroid monotherapy, but excluding radiation therapy).

Thalidomide, 100 mg, was orally administered once daily before bedtime every day for 4 weeks. As a general rule, the dose was increased by 100 mg at Weeks 5, 9, and 13 after starting treatment, and the treatment duration was 16 weeks. The "levels of response" as defined below were used as the criteria for evaluating efficacy.

a. Complete response (CR): Disappearance of M protein in serum or disappearance of M protein including Bence Jones protein in urine
b. Partial response (PR): Decrease of M protein in serum or decrease in Bence Jones protein in urine (by not less than 50% from baseline)
c. Minor response (MR): Decrease of M protein in serum or decrease in Bence Jones protein in urine (by not less than 25% from baseline)
d. No change (NC): Less than 25% decrease or increase in M protein from baseline without manifestation of new symptoms directly related to myeloma (bone lesion, plasmacytoma, renal disorder, anaemia, hypercalcaemia, leukemic change)
e. Progressive disease (PD): 25% or more increase in M protein, or less than 25% decrease or increase in M protein from baseline with manifestation of new symptoms directly related to myeloma (bone lesion, plasmacytoma, renal disorder, anaemia, hypercalcaemia, leukemic change)
f. Unevaluable

The dose was to be maintained, i.e. not increased, if the disease condition was MR or better as judged by the attending physician at Week 4, 8, or 12 (on the scheduled day or the next day) after starting treatment. If the "level of response" was judged to be unchanged while the treatment was continued at a maintained dose, the dose was to be increased by 100 mg at Weeks 8 and 12 after starting treatment. When Grade 2 non-hematological toxicity or Grade 3 hematological toxicity was observed, administration of the investigational drug was to be discontinued if 100 mg was being administered and, if 200 mg or higher doses were being administered, administration was to be continued at a dose 100 mg lower than before. If no symptom resolution or improvement was observed 1 week after the dose reduction, the dose was to be further decreased by 100 mg.

Patients with non-secretory MM were excluded from the study, and concomitant use of steroids such as dexamethasone and prednisolone (except external preparations) was prohibited.

The protocol was revised regarding the following 4 items on January 12, 2006, during the study period, but the applicant explained that none of these changes affected the results of the study.

a. FDP level in the exclusion criteria was changed from "not less than 5 μg/mL" to "not less than 5 μg/mL (i.e. the upper limit of the reference range set by the respective institution)." (Reason: The upper limit for FDP was not set at 5 μg/mL at 4 of 22 study sites.)
b. Study period was changed. (Reason: There was a delay in the procedure for study conduct at 1 study site, requiring extension of the study period by 3 months.)
c. The expiration period of the investigational drug was changed from 9 to 12 months. (Reason: Update to new expiration period determined pursuant to completion of up to 12 months of long-term testing of the drug product used for the clinical study.)
d. The method for calculating the M protein level was changed from "to be calculated by total protein × percentage of γ-globulin fraction" to "to be calculated by total protein × percentage of γ-globulin fraction (or fraction corresponding to M protein)." (Reason: Depending on the disease type of patients, M protein is not necessarily limited to the γ-globulin fraction. The change was made to adjust for such disease types.)

In total, 42 patients were enrolled, of whom 37 excluding 5 ineligible patients (4 withdrew before starting treatment, 1 met exclusion criteria) were judged to be eligible. Of these, 21 subjects completed the 16-week treatment, while 16 discontinued or dropped out of the study (9 subjects discontinued due to adverse drug reactions, 7 due to aggravation of symptoms). Three of the discontinued/drop-out subjects were not included in the efficacy analysis because they received study treatment for less than 4 weeks. As a result, 13 of the discontinued/drop-out subjects were included in the efficacy analysis. Therefore, a total of 34 subjects were included in the efficacy analysis population: all 21 subjects who completed the 16-week treatment and the 13 subjects included in the efficacy analysis among the discontinued/drop-out subjects. All 37 eligible patients were included in the safety analysis.

"Level of response," the primary efficacy endpoint, was evaluated using the method of Murakami, et al. (*Rinsho Ketsueki.* 2004;45:468-472) established based on the criteria of the Myeloma Task Force (*Cancer Chemother Rep 3 [Cancer Treat Rep].* 1973;4:145-148), according to the percent decrease from baseline of serum M protein or urinary Bence Jones protein at 2, 4, 6, 8, 10, 12, 14, and 16 weeks after the start of treatment, or at study discontinuation or drop-out.

Subjects with CR, PR, or MR at the final efficacy analysis were defined as "responders (those in whom a not less than 25% decrease in M protein from baseline persisted for 4 weeks or more)," and the percentage of responders was to be compared with the expected response rate. The applicant set the expected response rate at 42% and the threshold response rate at 7%, based on the data from a publication (*Jpn J Cancer Res.* 2002;93:1029-1036) in which a Thalidomide product different from the proposed product was used.

The responses in the 34 subjects in the efficacy analysis population were CR in 0, PR in 5 (14.7%), MR in 7 (20.6%), NC in 12 (35.3%), PD in 6 (17.6%), and unevaluable in 4 (11.8%), with the percentage of responders being 35.3% (95% CI [confidence interval], 19.8%-53.5%).

Adverse events occurred in all 37 subjects included in the safety analysis, and abnormal laboratory values were observed in 35 (94.6%). The major adverse events are listed in the table below. Of the ineligible patients, one who met the exclusion criteria (FDP exceeding the upper limit), but received study treatment, experienced Grade 2 eruption judged to be a noteworthy adverse event. Concomitant drugs administered were bisphosphonates in 22 subjects (59.5%), aspirin in 5 (13.5%), and warfarin in 2 (5.4%).

Adverse events for which a causal relationship to Thalidomide could not be denied (adverse drug

reactions) occurred in 37 subjects (100%). Adverse drug reactions with an incidence of 10% or more were constipation in 23 subjects (62.2%), sleepiness in 20 (54.1%), dry mouth in 16 (43.2%), fatigue in 11 (29.7%), tremor and eruption in 10 each (27.0%), numbness of lips in 8 (21.6%), dizziness, dysgeusia, and queasy in 7 each (18.9%), numbness of limbs, abdominal distension, and oedema in 6 each (16.2%), heaviness of head, sinus bradycardia, filmy vision, and malaise in 5 each (13.5%), and itchy skin and cold extremities in 4 each (10.8%).

Of the adverse reactions to Thalidomide, abnormal laboratory values with an incidence of 10% or more were neutrophil count decreased in 17 subjects (45.9%), white blood cell count decreased in 15 (40.5%), monocyte count increased, D dimer increased, and CRP increased in 12 each (32.4%), FDP increased in 11 (29.7%), gamma GTP decreased, basophil count increased, eosinophil count increased, and urinary protein positive in 10 each (27.0%), alpha 1 globulin increased, lymphocyte count decreased, and platelet count decreased in 7 each (18.9%), creatine kinase decreased in 6 (16.2%), BUN increased, sodium decreased, haemoglobin decreased, and total cholesterol decreased in 5 each (13.5%), and AST increased, ALT increased, alpha 2 globulin increased, creatinine increased, lymphocyte count increased, neutrophil count increased, red blood cell count decreased, and urine sugar positive in 4 each (10.8%).

List of adverse events by organ classification

Adverse events, organ classification	No. of subjects (%)	
	Adverse events	Adverse drug reactions
Skin and appendage disorders	20 (54.1%)	13 (35.1%)
Musculoskeletal disorders	11 (29.7%)	5 (13.5%)
Collagen disorders	0 (0%)	0 (0%)
Central and peripheral nervous system disorders	24 (64.9%)	23 (62.2%)
Autonomic nervous system disorders	2 (5.4%)	0 (0%)
Vision disorders	8 (21.6%)	5 (13.5%)
Hearing and vestibular disorders	0 (0%)	0 (0%)
Other special sensory disorders	10 (27.0%)	8 (21.6%)
Psychiatric disorders	23 (62.2%)	20 (54.1%)
Gastrointestinal disorders	32 (86.5%)	30 (81.1%)
Hepatobiliary disorders	24 (64.9%)	15 (40.5%)
Metabolism and nutrition disorders	36 (97.3%)	24 (64.9%)
Endocrine disorders	2 (5.4%)	1 (2.7%)
Cardiovascular disorders, general	4 (10.8%)	2 (5.4%)
Myo-, endo-, peri-cardial, and valve disorders	0 (0%)	0 (0%)
Heart rate and rhythm disorders	12 (32.4%)	8 (21.6%)
Vascular (extra-cardiac) disorders	9 (24.3%)	5 (13.5%)
Respiratory disorders	14 (37.8%)	4 (10.8%)
Red blood cell disorders	13 (35.1%)	7 (18.9%)
White blood cell and reticuloendothelial disorders	35 (94.6%)	27 (73.0%)
Platelet, haemorrhagic, and coagulation disorders	28 (75.7%)	19 (51.4%)
Urological disorders	27 (73.0%)	18 (48.6%)
Genital disorders, male	0 (0%)	0 (0%)
Genital disorders, female	0 (0%)	0 (0%)
Foetal disorders	0 (0%)	0 (0%)
Neonatal and infancy disorders	0 (0%)	0 (0%)
Neoplasm (tumour)	0 (0%)	0 (0%)
General disorders	35 (94.6%)	29 (78.4%)
Application site disorders	2 (5.4%)	0 (0%)
Resistance mechanism disorders	10 (27.0%)	0 (0%)
Secondary terms	0 (0%)	0 (0%)
Poisoning	0 (0%)	0 (0%)
Red blood cell disorders	13 (35.1%)	7 (18.9%)
Haematocrit decreased	3 (8.1%)	2 (5.4%)
Haematocrit increased	1 (2.7%)	0 (0%)
Haemoglobin decreased	10 (27.0%)	5 (13.5%)
Red blood cell count decreased	4 (10.8%)	4 (10.8%)
Anaemia	1 (2.7%)	0 (0%)

Major adverse events that occurred with an incidence of 10% or more are shown in the table below. Numbness, which included “numbness in face”, “numbness of limbs”, “numbness of upper extremities,” and “numbness of lips,” occurred in a total of 18 subjects (48.6%), and were all regarded as adverse drug reactions.

Adverse events with an incidence ≥ 10%

Adverse events	No. of subjects (%)		Adverse events	No. of subjects (%)	
	Adverse events	Adverse drug reactions		Adverse events	Adverse drug reactions
Constipation	24 (64.9%)	23 (62.2%)	Sinus bradycardia	6 (16.2%)	5 (13.5%)
Sleepiness	22 (59.5%)	20 (54.1%)	Common cold	7 (18.9%)	0 (0%)
Dry mouth	19 (51.4%)	16 (43.2%)	Headache	5 (13.5%)	3 (8.1%)
Tremor	12 (32.4%)	10 (27.0%)	Anxiety	5 (13.5%)	3 (8.1%)
Fatigue	12 (32.4%)	11 (29.7%)	Cold extremities	5 (13.5%)	4 (10.8%)
Dizziness	11 (29.7%)	7 (18.9%)	Cough	5 (13.5%)	1 (2.7%)
Eruption	10 (27.0%)	10 (27.0%)	Chest pain	5 (13.5%)	2 (5.4%)
Abdominal distension	10 (27.0%)	6 (16.2%)	Malaise	5 (13.5%)	5 (13.5%)
Dysgeusia	9 (24.3%)	7 (18.9%)	Weight decreased	5 (13.5%)	3 (8.1%)
Diarrhoea	9 (24.3%)	2 (5.4%)	Feeling of weakness	5 (13.5%)	3 (8.1%)
Queasy	9 (24.3%)	7 (18.9%)	Rash	4 (10.8%)	2 (5.4%)
Oedema	9 (24.3%)	6 (16.2%)	Movement disorder	4 (10.8%)	1 (2.7%)
Numbness of lips	8 (21.6%)	8 (21.6%)	Abdominal pain	4 (10.8%)	3 (8.1%)
Anorexia	8 (21.6%)	3 (8.1%)	Vomiting	4 (10.8%)	1 (2.7%)
Heaviness of head	7 (18.9%)	5 (13.5%)	Blood pressure increased	4 (10.8%)	2 (5.4%)
Filmy vision	7 (18.9%)	5 (13.5%)	Palpitations	4 (10.8%)	1 (2.7%)
Itchy skin	6 (16.2%)	4 (10.8%)	Epistaxis	4 (10.8%)	1 (2.7%)
Numbness of limbs	6 (16.2%)	6 (16.2%)	Choking sensation	4 (10.8%)	1 (2.7%)
Heartburn	6 (16.2%)	3 (8.1%)	Pneumonia	4 (10.8%)	0 (0%)

Abnormal laboratory values with an incidence ≥ 10% regarded as adverse drug reactions

Abnormal laboratory values	No. of subjects (%)	
	Adverse events	Adverse drug reactions
CRP increased	27 (73.0%)	12 (32.4%)
Neutrophil count decreased	21 (56.8%)	17 (45.9%)
Protein urine positive	21 (56.8%)	10 (27.0%)
Monocyte count increased	20 (54.1%)	12 (32.4%)
Creatine kinase decreased	18 (48.6%)	6 (16.2%)
Basophil count increased	18 (48.6%)	10 (27.0%)
Eosinophil count increased	18 (48.6%)	10 (27.0%)
White blood cell count decreased	17 (45.9%)	15 (40.5%)
Lymphocyte count decreased	16 (43.2%)	7 (18.9%)
D dimer increased	14 (37.8%)	12 (32.4%)
Gamma GTP decreased	13 (35.1%)	10 (27.0%)
FDP increased	12 (32.4%)	11 (29.7%)
Platelet count decreased	11 (29.7%)	7 (18.9%)
AST increased	10 (27.0%)	4 (10.8%)
BUN increased	10 (27.0%)	5 (13.5%)
Alpha 1 globulin increased	10 (27.0%)	7 (18.9%)
Haemoglobin decreased	10 (27.0%)	5 (13.5%)
Lymphocyte count increased	10 (27.0%)	4 (10.8%)
Total cholesterol decreased	10 (27.0%)	5 (13.5%)
ALT increased	9 (24.3%)	4 (10.8%)
Sodium decreased	9 (24.3%)	5 (13.5%)
Neutrophil count increased	9 (24.3%)	4 (10.8%)
Alpha 2 globulin increased	8 (21.6%)	4 (10.8%)
Creatinine increased	8 (21.6%)	4 (10.8%)
Urine sugar positive	8 (21.6%)	4 (10.8%)
Red blood cell count decreased	4 (10.8%)	4 (10.8%)

Death occurred in 1 subject. The causal relationship to Thalidomide was judged to be "unknown."

This subject (subject No. 32) was a 7[redacted]-year old male patient with IgG type MM. After approximately 1 month of treatment with 100 mg/day of Thalidomide, his condition worsened with increased serum calcium, resulting in discontinuation of treatment. One week after discontinuation of treatment, the patient developed gastrointestinal perforation, followed by pneumonia, etc., and he died of respiratory failure 2 weeks after discontinuation of treatment. The investigator judged the causal relationship to the investigational drug to be "unknown" due to lack of information such as autopsy findings sufficient for ruling out a causal relationship.

Non-fatal serious adverse events were observed in 5 subjects (pneumonia in 2, ischaemic heart disease, compression fracture of lumbar vertebra, and compression fracture of thoracic vertebra in 1 each). Of these, 1 patient (subject No. 26, ischaemic heart disease) complained of chest pain a week after starting study treatment and was diagnosed with ischaemic heart disease. Administration of 100 mg/day of Thalidomide had been continued until 1 day before the onset of chest pain, after which the patient discontinued the study due to this adverse event. Chest pain resolved the next day with nitrate administration, but the subject again complained of a chest pressure sensation 2 days later. The symptom was not resolved by nitrate on that occasion. This symptom was judged to be "probably related" to Thalidomide.

Foreign clinical studies of Thalidomide have shown that the drug causes venous thromboembolism (VTE) at a high incidence. In the Japanese clinical study, aspirin was used in 5 subjects (13.5%) and warfarin in 2 (5.4%) as a preventive measure. There were no subjects experiencing VTE.

Of the 16 subjects in whom study treatment was discontinued in the Japanese clinical study, 8 discontinued the study because of adverse events, in addition to the above 2 subjects. The adverse events that led to study discontinuation were judged to be adverse drug reactions in all 8 subjects (see table below).

List of subjects in whom discontinuation was due to adverse drug reactions other than death or serious adverse events (Japanese clinical study)

Age	Gender	Dose (mg)	Adverse event that led to discontinuation	Grade	Time of onset (Day)	Duration (days)	Outcome
6[redacted]	Female	100	Haemoglobin decreased	3	8	56	Not recovered
6[redacted]	Female	100	White blood cell count decreased	3	7	23	Recovered
7[redacted]	Female	200	Queasy, dysgeusia, weight decreased	1, 1, 1	31, 31, 42	40, 40, 29	Not recovered
7[redacted]	Male	100	Neutrophil count decreased	3	29	8	Recovered
7[redacted]	Female	100	White blood cell count decreased, haemoglobin decreased	3, 3	8, 8	3, 22	Recovered
6[redacted]	Female	100	Sinus bradycardia	2	55	17	Recovered
7[redacted]	Male	100	Urinary protein positive	2	64	21	Improved
4[redacted]	Female	200	Neutrophil count decreased	3	85	43	Improved

4.3.B *Outline of the review by the PMDA*

4.3.B.1) Review policy on Thalidomide

The PMDA regards the Japanese clinical study that produced the submitted evaluation data to have not adequately been designed to allow sufficient evaluation of the efficacy, safety, and dose and administration of Thalidomide. As a result, the information obtained from the study is extremely

limited.

Therefore, in addition to the descriptions in medical texts, treatment guidelines, publications, and the clinical track record of Thalidomide in patients with MM, both in Japan and foreign countries, the circumstances listed below were also taken into account in evaluating the proposed product:

a. There are currently no commonly agreed-upon standard therapies for relapsed or refractory MM, either in Japan or overseas. Also, there appear to be no significant differences between Japan and other countries in the treatment system or prognosis of the relevant patient population.
b. There appear to be no ethnic differences in the disease conditions of MM.
c. No ethnic difference has been reported regarding the pharmacokinetics of Thalidomide in humans.
d. The clinical course of MM is characterized by repeated cycles of progression and remission, and treatment options are limited for patients with relapse after, or without response to, the initial treatment.
e. As is evident from the fact that Thalidomide is designated as an orphan drug, it is anticipated to be difficult to accumulate data in clinical studies in Japan.
f. The efficacy of Thalidomide has been demonstrated in a Japanese clinical study, as judged by serum M protein level, commonly regarded as an index reflecting the tumor burden in published medical texts as well as in clinical practice. Thus, the product is expected to be useful in Japanese patients.
g. The proposed product is expected to be useful because it is administered orally and can thus be used on an outpatient basis.

Although no data on the efficacy as regards time to event, such as overall survival, is available for the proposed product, the PMDA decided to evaluate the usefulness of Thalidomide in a comprehensive manner by assessing the efficacy of Thalidomide based on the results of the Japanese clinical study, and by referring to the data from foreign published studies that investigated the efficacy of Thalidomide in patients with relapsed or refractory MM using Thalidomide products with formulations different from that of the proposed product, as complimentary information.

Deliberation at the Expert Discussion regarding the above decision of the PMDA is needed.

4.3.B.2) Efficacy index

In the Japanese clinical study of Thalidomide, the primary efficacy endpoint used was “level of response” defined as the decrease in the M protein level.

The PMDA asked the applicant to explain the reason for selecting the “level of response” as the index for the efficacy of anti-neoplastic agents against relapsed or refractory MM, instead of overall survival, etc.

The applicant responded as follows: In treating MM, it is critical to decrease the number of myeloma cells. Therefore, it is common in clinical practice to measure over time, as a tumor marker, the level of M protein produced specifically by myeloma cells and correlated with the number of such cells (tumor burden). Also, it has been reported in Japanese and foreign clinical studies (*N Engl J Med.* 1999;341:1565-1571, *Jpn J Cancer Res.* 2002;93:1029-1036) that the percent decrease in M protein with treatment has a certain correlation with the percent decrease in the number of bone marrow plasma cells. On the basis of these findings, it is considered possible to assess the efficacy of Thalidomide for MM treatment by evaluating the “level of response,” which is indicated by changes in M protein level over time.

The PMDA understands that the method of Murakami et al. (*Rinsho Ketsueki*. 2004;45:468-472), which was used as an assessment criterion for the "level of response" in the Japanese clinical study, has been used for retrospective evaluation of the use state and treatment results of Thalidomide preparations in member institutions of the "Japanese Society of Myeloma." However, the PMDA judges it possible to evaluate the changes in serum M protein as a measure for assessing the efficacy of Thalidomide, for the following reasons.

a. The EBMT/IBMTR/ABMTR response criteria (*Br J Haematol*. 1998;102:1115-1123), a set of response criteria for MM widely used internationally, require that all 4 of the following conditions are met for a judgment of CR: (a) no M protein is detected in serum or urine by immunofixation for a minimum of 6 weeks, (b) not more than 5% bone marrow plasma cells, as tested by bone marrow aspiration, (c) no increase in the size or number of osteolytic lesions (excluding compression fractures), and (d) disappearance of plasmacytoma in soft tissue. Thus, these criteria are more strict than those set by Murakami et al. in that evaluation includes changes in plasmacytoma and bone lesions, the ratio of plasma cells in bone marrow aspirate, and other indirect lesions (renal disorder, hypercalcaemia, etc.), as well as changes in the observed level of M protein. However, the EBMT/IBMTR/ABMTR response criteria are designed to evaluate treatment efficacy in patients given high-dose chemotherapy or hematopoietic stem cell transplantation, and are not necessarily suitable for evaluating salvage therapy for relapsed or refractory MM, the target disease in the Japanese clinical therapy.

b. International Myeloma Working Group Uniform Response Criteria (*Leukemia*. 2006;20:1467-1473) (IWMG criteria) have not been validated to date
(National Comprehensive Cancer Network [NCCN] Guideline v2, 2008;
http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf [as of July 2008]).

c. In recent publications (e.g. *N Engl J Med*. 1999;341:1565-1571, *Br J Haematol*. 2004;125:149-155, *J Clin Oncol*. 2003;21:2732-2739) of studies on the efficacy and safety of Thalidomide as a salvage therapy for MM, the assessment criteria for tumor size reduction were not standardized, suggesting that no consensus is currently available for such criteria.

d. The serum M protein level is regarded as an excellent tumor marker (*Harrison's Principles of Internal Medicine*. 17th ed. USA: McGraw Hill; 2008).

e. The M protein level is used as an index reflecting the tumor burden in clinical practice in Japan and overseas.

f. In multiple publications (e.g. *N Engl J Med*. 1999;341:1565-1571, *Haematologica*. 2002;87:408-414, *Semin Oncol*. 2002;29:34, *Hematology J*. 2002;3:185-192), M protein is included among the response criteria.

Nevertheless, the PMDA considers as follows: Decreased serum M protein is not observed until 4 to 6 weeks after the improvement of clinical symptoms (*Harrison's Principles of Internal Medicine*. 17th ed. USA: McGraw Hill; 2008). In addition, in the Japanese clinical study, the serum M protein level was calculated by multiplying the total protein level by the percentage of γ-globulin fraction (fraction corresponding to M protein), a method likely less accurate than immunofixation. Furthermore, according to the applicant, bone marrow aspiration and X-ray examination were not included in the protocol of the Japanese clinical study, due to the physical burden on patients, but this explanation does not justify the exclusion of such tests. These tests and evaluations should also have been done in this Japanese clinical study.

In addition, there are reports on cases with increased extramedullary mass sizes accompanied by decreased M protein (*Br J Haematol.* 2004;101:101-103) and similar findings, suggesting that efficacy evaluation based solely on decreased M protein has a limitation. Therefore, times to events such as death and progression (overall survival, disease-free survival, time to progression, etc.) should have been investigated in evaluating treatment efficacy.

Regarding the justification for setting the treatment duration (16 weeks) and dose escalation schedule (every 4 weeks), the applicant explained as follows, citing multiple publications:
The 16-week period is sufficient for evaluating short-term efficacy and safety. Dose increases of 100 mg every 4 weeks were set by referring to the dosage regimen (weekly dose increase) in Australia and New Zealand where a Thalidomide product with a formulation different from that of the proposed product has been approved for MM.

Given that the proposed product is used as a salvage therapy in patients with relapsed or refractory MM for which there is no established standard therapy, the drug is likely to be administered for a long period to patients who respond to the treatment. Therefore, the PMDA considers the 16-week observation period not to be sufficiently long. Also, since the dose escalation schedule for the Japanese clinical study and the dosage regimen approved in Australia differ from each other, it is not appropriate to justify the dose escalation schedule in the Japanese clinical study based on the dosage regimen approved overseas.

There is a report stating that the total dose of Thalidomide over 3 months is significantly associated with overall survival (*Clin Cancer Res.* 2002;8:3377-3382). Therefore, it will be necessary, after marketing, to collect data on long-term efficacy and safety including the times to events such as death.

Deliberation should be made at the Expert Discussion to reach a final conclusion regarding the above judgment of the PMDA.

4.3.B.3) Efficacy
The activity of the proposed product to reduce the M protein level remained overall favorable up to 16 weeks of treatment in the Japanese clinical study, and this activity did not differ significantly from those of other Thalidomide products reported overseas, from which the proposed product is expected to be useful in Japanese patients with MM. In addition, whereas most of the drugs indicated for MM are injectable formulations, the proposed product is an oral formulation that is easily administered on an outpatient basis. Based on these facts, the PMDA has concluded that the proposed product is well worth supplying for clinical practice in Japan as a treatment option for relapsed or refractory MM.

Deliberation should be made at the Expert Discussion to reach a final conclusion regarding the above judgment of the PMDA.

4.3.B.3).(1) Serum M protein-reducing effect
In the protocol of the Japanese clinical study, the expected response and threshold response rates were set at 42% and 7%, respectively, based on the response rate (42%) in a Japanese study (*Jpn J Cancer Res.* 2002;93:1029-1036) which used the serum M protein level change as an index and on the placebo effect (range, 0%-7%) in a foreign review (*J Natl Cancer Inst.* 2003;95:19-29).

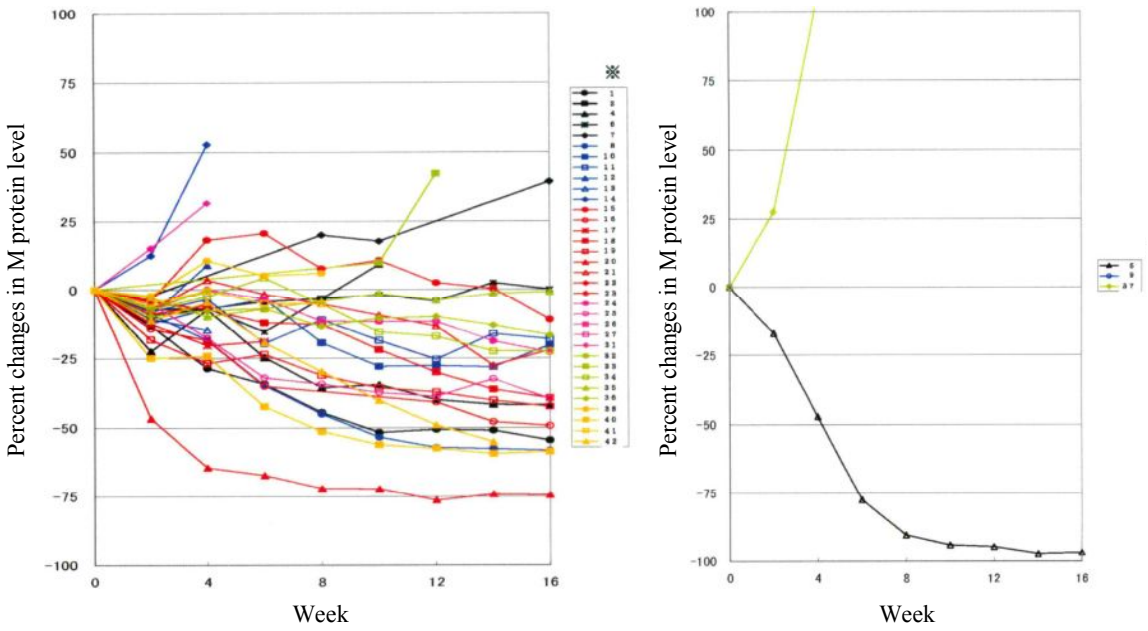
The response rate at the final efficacy analysis (CR + PR + MR, i.e. the number of subjects in whom a $\geq$ 25% decrease in serum M protein level from baseline persisted for $\geq$ 4 weeks) was 35.3% (95% CI, 19.8%-53.5%) (12 of 34 subjects), with the lower limit of the 95% CI exceeding the threshold response rate (7%). Decreases in the M protein level at each evaluation time point are shown in the table below.

Decreases in M protein level at each evaluation time point

	No. of subjects studied	No. of subjects (%)						
		CR	PR	MR	NC	PD	Unevaluable	MR or better
At 2 weeks after starting treatment	34	0	0	2 (5.9)	29 (85.3)	1 (2.9)	2 (5.9)	2 (5.9)
At 4 weeks after starting treatment	30	0	1 (3.3)	3 (10.0)	22 (73.3)	1 (3.3)	3 (10.0)	4 (13.3)
At 6 weeks after starting treatment	27	0	2 (7.4)	5 (18.5)	17 (63.0)	0	3 (11.1)	7 (25.9)
At 8 weeks after starting treatment	25	0	3 (12.0)	6 (24.0)	14 (56.0)	0	2 (8.0)	9 (36.0)
At 10 weeks after starting treatment	22	0	5 (22.7)	5 (22.7)	11 (55.0)	0	1 (4.5)	10 (45.5)
At 12 weeks after starting treatment	22	0	5 (22.7)	8 (36.4)	7 (31.8)	0	2 (9.1)	13 (59.1)
At 14 weeks after starting treatment	21	0	5 (23.8)	7 (33.3)	7 (33.3)	0	2 (9.5)	12 (57.1)
At 16 weeks after starting treatment	21	0	5 (23.8)	5 (23.8)	9 (42.9)	1 (4.8)	1 (4.8)	10 (47.6)
At 16 weeks after starting treatment or at discontinuation	34	0	6 (17.6)	5 (14.7)	17 (50.0)	5 (14.7)	1 (2.9)	11 (32.4)

Changes in the M protein level over time in individuals are shown in the figure below. The PMDA judges that the M protein level tends to decrease in most subjects receiving Thalidomide.

Changes in M protein level by subject (left, serum M protein; right, urinary M protein)



The PMDA instructed the applicant to re-evaluate the efficacy analysis population according to the International Myeloma Working Group Uniform Response Criteria (*Leukemia*. 2006;20:1467-1473), although immunofixation and free light chain assay were not performed in the Japanese clinical study, to which the applicant answered that CR was 0%, PR 18.2% (6 of 33 subjects), SD 63.6% (21 of 33 subjects), and PD 18.2% (6 of 33 subjects).

M protein-reducing effects of Thalidomide monotherapy in patients with relapsed or refractory MM confirmed by the PMDA to have been reported in major publications are shown in the table below. The PMDA has confirmed that the results of the Japanese clinical study were not significantly different from those in these publications although the Thalidomide products used in these clinical studies appear to have formulations different from that of the proposed product.

M protein-reducing effect of Thalidomide monotherapy

Cited publication	Dose	No. of subjects	Percent decrease in M protein level				
			> 75%	50%-75%	25%-50%	SD/no response	PD
N Engl J Med. 1999;341:1565-1571	200–800	84	14 (17%)	7 (8%)	6 (7%)	57 (68%)	
Blood. 1999;94(suppl 1):604a [abstract 2686]	200-800	44	11 (25%)		33 (75%)		
Blood. 1999;94(suppl 1):316a [abstract 1413]	50-400	33	4 (12%)	8 (24%)	21 (64%)		
Blood. 1999;94(suppl 1):316a [abstract 1414]	200-800	14	3 (21%)		1 (7%)	5 (36%)	5 (36%)
Mayo Clin Proc. 2000;75:897-901	200-800	16		4 (25%)	1 (6%)	5 (31%)	6 (38%)
Br J Haematol. 2000;108:391-393	200-800	17	5 (29%)	5 (29%)	1 (6%)	1 (6%)	5 (29%)
Br J Haematol. 2000;109:89-96	200-800	23	10 (43%)		6 (26%)		7 (30%)
Semin Oncol. 2001;28:588-592	100-800	23	3 (13%)		9 (39%)	2 (9%)	9 (39%)
Br J Haematol. 2001;115:605	100-400	51	9 (18%)		17 (33%)	14 (27%)	11 (22%)
Blood. 2001;98:492-494*	200–800	169	20%	10%	7%	63%	
Haematologica. 2001;86:409-413	100-800	11	1 (9%)	3 (27%)	4 (36%)	3 (27%)	
Haematologica. 2001;86:404-408	200-400	53	7 (13%)	12 (23%)	8 (15%)	4 (8%)	22 (42%)
Semin Oncol. 2002;29(6 suppl 17):34-38	50-200	36	6 (17%)	3 (8%)	7 (19%)	0 (0%)	20 (56%)
Hematol J. 2002;3:185-192	50-800	83	11 (13%)	29 (35%)	15 (18%)	13 (16%)	15 (18%)
Haematologica. 2002;87:408-414	100-800	65	5 (8%)	12 (18%)	11 (17%)	18 (28%)	19 (29%)
Leuk Lymphoma. 2002;43:351-354	50-500	12	3 (25%)	2 (17%)	2 (17%)	4 (33%)	1 (8%)
Mayo Clin Proc. 2003;78:34**	200–800	32	10 (31%)		7 (22%)	10 (31%)	4 (13%)
Leuk Res. 2003;27:909-914	100-600	69	7 (10%)	12 (17%)	15 (22%)	35 (51%)	
Leukemia. 2005;19:156-159	100-400	32	19 (59%)		6 (19%)	6 (19%)	1 (3%)
Bone Marrow Transplant. 2005;35:165-169***	50-600	31	3 (10%)	6 (19%)	0 (0%)	9 (29%)	12 (39%)
Acta Haematol. 2006;116:70-71	50-100	18	3 (17%)	5 (28%)	3 (17%)	3 (17%)	4 (22%)
Japanese clinical study***	100-400	34	0	6 (17.6%)	5 (14.7%)	17 (50.0%)	5 (14.7%)

*, number of subjects not provided; **, unconfirmed PR in 1 subject; ***, unevaluable in 1 subject

Based on the above, the PMDA has concluded that the drug is expected to be effective as indicated by decreased serum M protein level because the submitted study results show that treatment with Thalidomide reduced the tumor burden in some subjects with relapsed or refractory MM.

4.3.B.3).(2) Laboratory values related to bone lesions

Since osteolytic lesions are the major bone lesions in MM and are frequently accompanied by hypercalcaemia, and ALP is also used as an index for the activity of osteoblasts, the PMDA asked the applicant about the laboratory changes related to bone lesions.

The applicant submitted the following table.

Laboratory changes related to bone (34 subjects included in the efficacy analysis)

	No. of subjects	Calcium (mg/dL)	Adjusted calcium* (mg/dL)	ALP (IU/L)	ALB (g/dL)
Baseline	34	9.27 ± 0.77	9.34 ± 0.92	244.5 ± 150.9	4.16 ± 0.43
At 2 weeks after starting treatment	34	8.96 ± 0.81	9.12 ± 1.00	221.9 ± 109.9	3.93 ± 0.44
At 4 weeks after starting treatment	30	9.10 ± 0.60	9.16 ± 0.58	237.9 ± 101.3	4.13 ± 0.36
At 6 weeks after starting treatment	28	9.04 ± 0.62	9.14 ± 0.63	256.8 ± 110.9	4.00 ± 0.37
At 8 weeks after starting treatment	27	8.97 ± 0.54	9.10 ± 0.49	261.8 ± 119.2	3.98 ± 0.43
At 10 weeks after starting treatment	23	8.98 ± 0.46	9.04 ± 0.42	268.5 ± 160.6	4.09 ± 0.30
At 12 weeks after starting treatment	22	9.01 ± 0.56	9.11 ± 0.50	276.3 ± 172.4	4.05 ± 0.36
At 14 weeks after starting treatment	21	9.00 ± 0.59	9.09 ± 0.54	276.1 ± 158.0	4.07 ± 0.38
At 16 weeks after starting treatment	21	9.00 ± 0.56	9.06 ± 0.52	270.0 ± 144.5	4.13 ± 0.35
At 16 weeks after starting treatment or at discontinuation	34	9.19 ± 1.06	9.30 ± 1.24	254.8 ± 124.7	4.07 ± 0.47
P value		0.5427	0.7944	0.6499	0.1712

Mean ± SD, *P* value (baseline vs. 16 weeks after starting treatment or at discontinuation) (paired t-test)

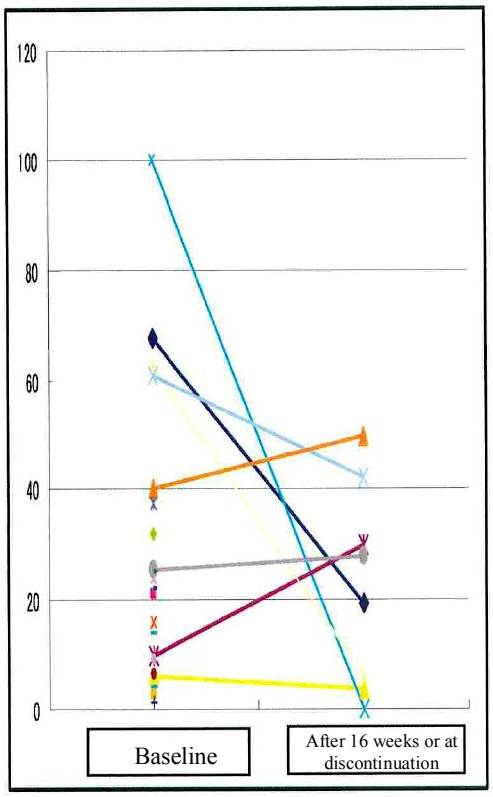
* Albumin-adjusted calcium

Although the adjusted serum calcium tends to decrease slightly, and ALP tends to increase, over time during treatment with Thalidomide, the PMDA considers it difficult to draw a definite conclusion from these results. In the Japanese clinical study, concomitant use of bisphosphonates was not prohibited, and they were actually used in 22 subjects (59.5%), possibly affecting the observed results. Therefore, the PMDA concluded that it is impossible to evaluate the effects of Thalidomide on laboratory values related to bone lesions.

4.3.B.3).(3) Effects on bone marrow plasma cells

Since bone marrow aspiration is highly invasive and painful for patients, the applicant considered it difficult to obtain informed consent. Therefore, the protocol stipulated that bone marrow aspiration be performed if necessary as an index of primary disease progression, before the start and after the completion of study treatment. Bone marrow aspirates were to be observed for the percentage of bone marrow plasma cells, and no information on the total cell number, megakaryocyte count, or fractions is available.

The percentage of bone marrow plasma cells of subjects who underwent bone marrow aspiration is shown in the following table and figure.



Subject No.	Baseline (%)	After 16 weeks or at discontinuation (%)	Response
1	67.6	19.5	PR
2	20.6	21.0	NC
4	6.1	3.6	MR
5	100.0	0.0	PR
6	10.0	30.0	NC
8	6.6	Not performed	PR
9	1.4	Not performed	Unevaluable
12	22.0	Not performed	Unevaluable
13	4.0	Not performed	Unevaluable
18	32.2	Not performed	MR
19	30.8	Not performed	MR
20	62.4	6.0	PR
21	61.0	42.2	NC
22	24.0	Not performed	Unevaluable
24	9.2	Not performed	NC
25	14.0	Not performed	MR
26	38.8	Not performed	Excluded from evaluation
31	10.8	Not performed	PD
33	31.8	Not performed	PD
34	2.8	Not performed	NC
35	40.2	49.8	NC
36	16.0	Not performed	NC
37	37.5	Not performed	PD
38	25.4	27.8	NC
40	1.2	Not performed	PR
42	25.2	Not performed	MR

The method for testing the percentage of bone marrow plasma cells, as presented by the applicant, included histopathological examination, smear test, and determining cell surface markers using flow cytometry, such that calculation methods varied among subjects. In some subjects, the percentage of plasma cells decreased markedly, while in others the M protein-reducing effect was not consistent with the decrease in the percentage of plasma cells. In addition, many patients did not undergo bone marrow aspiration. From these results, the PMDA concluded that it is difficult to evaluate the effects of Thalidomide on bone marrow plasma cells.

4.3.B.3).(4) Red blood cell-increasing effect

The applicant explained as follows:

Blood hemoglobin gradually increased and anaemic tendencies showed improvement (baseline vs. after 16 weeks or at discontinuation, 10.35 ± 2.01 g/dL vs. 10.91 ± 1.97 g/dL). At the same time, both the red blood cell count (3.260 ± 0.710 × 10^6/μL vs. 3.556 ± 0.775 × 10^6/μL) and hematocrit (31.89 ± 6.11% vs. 34.13 ± 6.26%) also tended to increase.

Changes in red blood cell count, hemoglobin, and hematocrit over time

	Red blood cell count ($\times 10^6/mm^3$)		Hemoglobin (g/dL)		Hematocrit (%)	
	No. of subjects	Mean ± SD	No. of subjects	Mean ± SD	No. of subjects	Mean ± SD
Baseline	37	3.26 ± 0.71	37	10.35 ± 2.01	37	31.89 ± 6.11
At 2 weeks after starting treatment	36	3.18 ± 0.69	36	10.15 ± 2.01	36	31.19 ± 5.98
At 4 weeks after starting treatment	31	3.40 ± 0.63	31	10.75 ± 1.72	31	33.18 ± 5.30
At 6 weeks after starting treatment	28	3.45 ± 0.65	28	10.79 ± 1.70	28	33.58 ± 5.33
At 8 weeks after starting treatment	27	3.59 ± 0.59	27	11.06 ± 1.50	27	34.62 ± 4.88
At 10 weeks after starting treatment	23	3.76 ± 0.57	23	11.51 ± 1.48	23	35.86 ± 4.54
At 12 weeks after starting treatment	22	3.81 ± 0.57	22	11.58 ± 1.44	22	36.23 ± 4.59
At 14 weeks after starting treatment	21	3.93 ± 0.48	21	11.79 ± 1.19	21	37.00 ± 3.68
At 16 weeks after starting treatment	21	3.99 ± 0.53	21	11.93 ± 1.22	21	37.48 ± 3.84
At 16 weeks after starting treatment or at discontinuation	37	3.56 ± 0.78	37	10.91 ± 1.97	37	34.13 ± 6.26

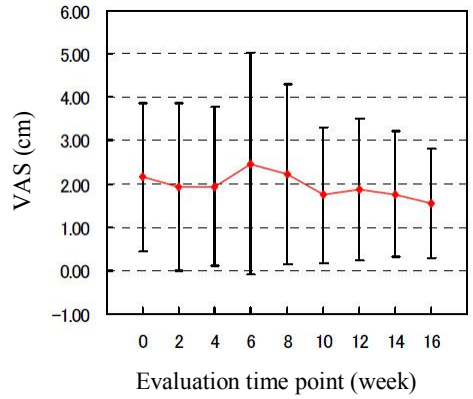
The PMDA asked the applicant whether the observed increase in red blood cell count was a direct action of Thalidomide or was due to the drug's suppressive effect on tumor growth.

The applicant responded as follows:
Although there is a report attributing the observed hemoglobin increase to an antitumor effect [Note by PMDA: Original sentence was "which are consistent with the presence of a true antitumor effect"] (*N Engl J Med.* 1999;341:1565-1571), there is no reported pharmacological study on Thalidomide demonstrating that it directly increases red blood cell count. Therefore, the increase is considered to be a change accompanying the drug's suppressive effect on tumor growth.

Lenalidomide, a Thalidomide analog, reportedly improves anaemia in myelodysplastic syndrome with 5q deletion syndrome (*N Engl J Med.* 2005;352:549-557). However, the PMDA considers the mechanism by which Thalidomide improves anaemia in patients with MM to be unclear at present.

4.3.B.3).(5) Bone pain
The applicant explained that bone pain, evaluated using the visual analog scale (VAS), was 1.64 ± 1.77 cm at baseline and 1.25 ± 1.44 cm after 16 weeks or at discontinuation, showing a tendency for improvement.

The PMDA asked the applicant to explain changes over time in bone pain in individual patients, to which the applicant responded as follows.



	No. of subjects	Mean ± SD
Baseline	28	2.15 ± 1.71
At 2 weeks after starting treatment	28	1.93 ± 1.93
At 4 weeks after starting treatment	23	1.94 ± 1.84
At 6 weeks after starting treatment	22	2.46 ± 2.56
At 8 weeks after starting treatment	22	2.21 ± 2.08
At 10 weeks after starting treatment	18	1.74 ± 1.57
At 12 weeks after starting treatment	17	1.87 ± 1.64
At 14 weeks after starting treatment	17	1.76 ± 1.45
At 16 weeks after starting treatment	17	1.55 ± 1.26
At 16 weeks after starting treatment or at discontinuation	36	1.25 ± 1.44

Given that bone pain evaluation was not performed in all subjects and that, in the Japanese clinical study, concomitant use of bisphosphonates was not prohibited and they were used in 22 subjects (59.5%), the PMDA considers it difficult to evaluate the effect of Thalidomide in reducing bone pain.

4.3.B.3).(6) Relationship between prognostic factors and efficacy

The applicant explained prognostic factors as follows:

According to the *Guideline for the treatment of multiple myeloma.* 1st edition (Japanese Society of Myeloma, ed. Bunkodo; 2004), decreased platelet count, dysplasia of bone marrow cells, low levels of serum albumin, abnormal LDH, abnormal CRP, hypercalcaemia, and serum creatinine level ≥ 2 mg/dL are regarded as poor prognostic factors. Also, there is a report which states that age, PS, β_2-microglobulin (β_2-MG), serum creatinine, LDH, CRP, serum albumin, hemoglobin, platelet count, plasma cell labeling index, plasma cell morphology, abnormality of chromosome 13, and extramedullary lesions detected by systemic FDG/PET scan are prognostic factors (*Hematology J.* 2003;4:379-398). In contrast, there is no report on prognostic factors focusing on the efficacy of Thalidomide.

The PMDA asked the applicant to explain the relationships of the efficacy of Thalidomide with patient background or prognostic factors.

The applicant answered that the Japanese clinical study showed no clear relationship of the efficacy of Thalidomide with patient background or prognostic factors.

Response rate to Thalidomide in each patient stratum was as shown in the following table.

M protein-reducing effect stratified by baseline characteristic

Parameter		No. of subjects	No. of subjects with M protein reduction showing MR or better	Response rate (%)	*P* value (Fisher's exact test)
Disease type	IgG type	20	8	40.0	0.86
	IgA type	11	3	27.3	
	B-J type	3	1	33.3	
Gender	Male	13	6	46.2	0.462
	Female	21	6	28.6	
Age (years)	40-49	4	3	75.0	0.25
	50-59	10	4	40.0	
	60-69	9	3	33.3	
	≥ 70	11	2	18.2	
Disease duration (years)	< 3	9	4	44.4	0.746
	≥ 3, < 5	14	6	42.9	
	≥ 5, < 10	7	1	14.3	
	≥ 10	3	1	33.3	
	Unknown	1	0	0	
PS	0	20	9	45.0	0.064
	1	13	2	15.4	
	2	1	1	100	
Autologous hematopoietic stem cell transplantation	No	18	6	33.3	1.000
	Yes	16	6	37.5	
β_2-MG (mg/L)	< 3.5	23	8	34.8	1.000
	≥ 3.5, < 5.5	4	1	25.0	
	≥ 5.5	7	3	42.9	
Albumin (g/dL)	< 3.5	1	0	0	1.000
	≥ 3.5	33	12	36.4	
Abnormal LDH	No	26	9	34.6	1.000
	Yes	8	3	37.5	
Abnormal CRP	No	29	9	31.0	0.319
	Yes	5	3	60.0	
Hemoglobin (g/dL)	< 8.5	6	2	33.3	1.000
	≥ 8.5, < 10	4	1	25.0	
	≥ 10	24	9	37.5	
Creatinine (mg/dL)	< 2.0	34	12	35.3	Not testable
	≥ 2.0	0	0	-	
Platelet count (/mm^3)	< 10×10^4	3	0	0	0.537
	≥ 10×10^4	31	12	38.7	
Calcium (mg/dL)	< 11	32	11	34.4	1.000
	≥ 11	2	1	50.0	

The PMDA asked the applicant to explain the efficacy of Thalidomide in MM patients with poor prognostic factors, such as t(4;14), t(14;16), 17p–, an abnormality of chromosome 13, hypodiploidy, hyper β_2-microglobulinaemia (≥ 3.5 mg/L), and hypoalbuminaemia (< 3.5 g/dL) (*J Clin Oncol.* 2005;23:3412-3420) or an extramedullary mass (amyloidoma) (*Hematology Am Soc Hematol Educ Program.* 2007).

The applicant responded as follows:
The patients enrolled in the Japanese clinical study did not include those who were definitely identified as having t(4;14), t(14;16), 17p-, an abnormality of chromosome 13, hypodiploidy, or an extramedullary mass (amyloidoma), but included 11 patients with hyper β_2-microglobulinaemia ($\geq$ 3.5 mg/L) and 1 patient with hypoalbuminaemia (< 3.5 g/dL). The table below shows the change over time in M protein decrease in these patients.

M protein-reducing effect in patients
with hyper β_2-microglobulinaemia or hypoalbuminaemia

Subject No.	β_2-MG (mg/L)	Albumin (g/dL)	Percent changes in M protein level							
			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16 or at discontinuation
2	4.31	4.22	-9.6	-7.0	-4.4	-3.3	-	-	-	9.2
5	8.10	3.92	-17.2	-47.2	-77.5	-90.5	-94.1	-94.7	-97.2	-96.8
8	10.24	4.26	-9.1	-18.5	-34.7	-45.1	-53.4	-57.0	-57.5	-58.0
20	4.30	4.15	-46.7	-64.3	-67.1	-72.0	-72.1	-76.4	-74.1	-74.4
21	5.80	4.18	-7.4	3.5	-1.6	-5.4	-9.5	-13.5	-27.7	-22.2
22	6.05	4.34	-9.1	-5.6	*	-	-	-	-	-6.7
32	6.40	2.33	-6.37	-	-	-	-	-	-	-0.65
33	3.60	3.98	*	*	*	*	9.9	-	-	42.4
36	5.72	4.13	-9.7	-7.8	-7.0	-13.6	-10.6	-10.0	-13.2	-16.9
40	5.98	3.98	-25.1	-24.3	-42.4	-51.3	-56.1	-57.4	-59.3	-58.5
41	4.61	3.82	-5.0	-0.4	-5.1	-5.3	-	-	-	-1.3

The PMDA further asked the applicant to classify all subjects investigated in the Japanese clinical study according to the International Staging System (ISS) (*J Clin Oncol.* 2005;23:3412-3420) and to explain the efficacy of Thalidomide, assessed by the serum M protein level as an index, for each of the strata.

The applicant submitted the following table.

Serum M protein-reducing effect of Thalidomide by ISS

		No. of subjects	CR	PR	MR	NC	PD	Unevaluable
Stage I	β_2-MG < 3.5 mg/L and albumin $\geq$ 3.5 g/dL	21	0 (0)	0 (0)	6 (28.6%)	8 (38.1%)	4 (19.0%)	3 (14.3%)
Stage II	Other than I and III	6	0 (0)	2 (33.3%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	0 (0)
Stage III	β_2-MG > 5.5 mg/L	7	0 (0)	3 (42.9%)	0 (0)	2 (28.6%)	1 (14.3%)	1 (14.3%)

The PMDA also considers it necessary to investigate the relationships of the efficacy of Thalidomide with background or prognostic factors by collecting information after marketing of the proposed product.

4.3.B.4) Safety
The protocol of the Japanese clinical study had stipulated that adverse events be evaluated according to the Common Terminology Criteria for Adverse Events v3.0, whereas the results were analyzed and reported using 2 sets of standard dictionaries, MedDRA/J and the Japanese Adverse Drug Reaction Terminology (J-ART).

The PMDA, upon examining the safety of Thalidomide, has judged that, in administering the drug, cautions should be exercised regarding nerve disorder, deep venous thromboembolism, tendencies for lethargy/somnolence, orthostatic hypotension, inhibition of angiogenesis, eruption, constipation, hypothyroidism, teratogenicity (Thalidomide embryopathy), and bone marrow depression, etc., and that preventive measures should be taken against these adverse events. The safety information included in the submitted evaluation data from the Japanese clinical study was only up to 16-week treatment, and as of the date of the present regulatory review, additional safety information is available from only 20 subjects who have proceeded to the extension study (maximum treatment duration, 116 weeks). Therefore, the PMDA considers it necessary to collect additional information after marketing, including safety information on the use of the proposed product for a longer period.

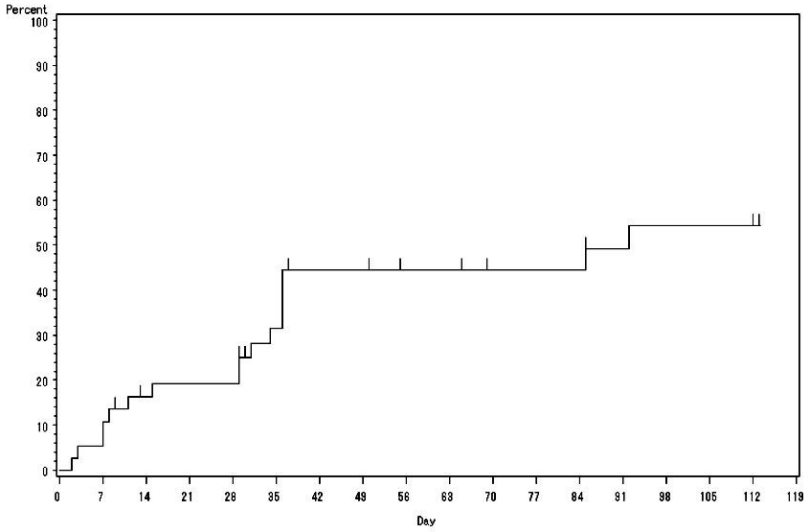
4.3.B.4).(1) Peripheral nerve disorders

Thalidomide is regarded as an anti-neoplastic agent that causes peripheral nerve disorders at a high frequency (*Cancer Principles and Practice of Oncology*. 8th ed. PA, USA: Lippincott Williams & Wilkins; 2008). In the Japanese clinical study, peripheral nerve disorders such as "numbness in face" occurred in a total of 18 subjects (48.6%) and all were judged to be adverse drug reactions.

The PMDA asked the applicant to explain the relationship between the total dose or number of doses and the incidence of peripheral nerve disorders.

The applicant responded as follows:

a. Peripheral nerve disorders tend to develop during the early phase of treatment (see figure below).
b. There is no relationship between the total dose and the incidence of peripheral nerve disorders.
c. The adverse event may also occur immediately after a dose increase (after 1 week).



Kaplan-Meier curve showing the incidence of peripheral nerve disorders

The PMDA considers as follows:

The applicant's explanation is based on the Japanese clinical study results which were obtained from an analysis of limited data. Patients with relapsed or refractory MM may have been affected by previous treatment with drugs such as vincristine sulfate that are known to cause peripheral nerve disorders, or may have developed peripheral nerve disorders accompanying MM, such as

amyloidosis. Therefore, it will be difficult to evaluate the relationship between peripheral nerve disorders and treatment with Thalidomide. In the Japanese clinical study, numbness developed in approximately half of the subjects although there were no severe peripheral nerve disorders or any that resulted in discontinuation of treatment. Also, since there is no information available on changes over time in neurological symptoms or their outcomes after long-term treatment with Thalidomide, it will be necessary to continue collecting information after marketing as well.

4.3.B.4).(2) VTE

Patients with MM may develop coagulopathy due to increased paraproteins; coagulation-related complications are observed in 15% of patients with IgG MM and in not less than 33% of those with IgA MM (*Cancer Principles and Practice of Oncology*. 8th ed. PA, USA: Lippincott Williams & Wilkins; 2008, *Semin Thromb Hemost*. 2003;29:275-282). Also, treatment of MM reportedly further augments hypercoagulation, as exemplified by the fact that VTE is reported in 12% to 24% of patients treated with Thalidomide, in particular in combination with dexamethasone or other anti-neoplastic agents (*Cancer Principles and Practice of Oncology*. 8th ed. PA, USA: Lippincott Williams & Wilkins; 2008, *Blood*. 2001;98:1614-1615). Therefore, the PMDA considers it necessary to pay attention to the possible occurrence of VTE in administering Thalidomide to patients with MM in Japan.

Although no VTE cases were reported in the Japanese clinical study, adverse event of FDP increased occurred in 12 subjects (32.4%), in 11 (29.7%) of whom a causal relationship between the adverse event and Thalidomide could not be denied.

Regarding the 1 subject for whom FDP increased was judged to be unrelated to the drug, the applicant explained as follows:
The increase in FDP was slight (from 3.3 μg/mL to 5.0 μg/mL), and the level returned to within the normal range (4.1 μg/mL) at the examination following a dose increase to 200 mg/day. Although the dose was increased by 100 mg/day each at Week 9 and weekly from Week 13, the FDP level remained within the reference range during the period from 5 to 16 weeks after starting treatment. From these findings, the increase in FDP was judged to be unrelated to Thalidomide.

The PMDA accepted the applicant's explanation.

The PMDA then confirmed that adverse event of D dimer increased was observed in 14 subjects (37.8%), in 12 (32.4%) of whom a causal relationship between the adverse event and Thalidomide could not be denied.

Regarding the 2 subjects for whom D dimer increased was judged to be unrelated to Thalidomide, the applicant explained as follows:
The investigator judged the adverse event to be unrelated to the investigational drug because the increase was "a temporary physiological change" (subject No. 16) and "within the physiological range" (subject No. 31). In subject No. 16, an increase in D dimer was observed only once and returned to within the reference range when examined in the following and subsequent weeks. In subject No. 31, the D dimer level was within the reference range at the time of discontinuation of treatment.

The PMDA considers as follows:
Subject No. 16 discontinued administration of 200 mg/day of the investigational drug because of Grade 2 pneumonia (unrelated to the drug), and the D dimer level returned to within the normal range (from 1.7 μg/mL to 0.7 μg/mL) upon withdrawal, which suggests that a causal relationship between the increase and Thalidomide cannot be denied. In subject No. 31, although the D dimer level was within the reference range at discontinuation of treatment, it was still higher than the baseline, showing that it is inappropriate to judge the increase as unrelated to the drug. Thus, it

will be appropriate to consider that a causal relationship to Thalidomide cannot be denied in any of the 14 subjects (37.8%) experiencing D dimer increased.

According to a foreign report, a total of 1118 VTE cases were reported spontaneously to the FDA MedWatch during the period from 1998 through July 2006. Also, in phase II/III studies and observational studies conducted in the US, the EU, and Australia, VTE was reported in 585 (12%) out of 4862 patients treated with Thalidomide. The incidences of VTE in 4068 patients with MM among them were 3% (95% CI, 2%-4%) (25 of 986 patients) in those receiving Thalidomide alone, 10% (95% CI, 9%-12%) (162 of 1544) in those receiving the combination of Thalidomide and dexamethasone, 12% (95% CI, 3%-21%) (6 of 50) in those receiving the combination of Thalidomide and doxorubicin hydrochloride, 19% (95% CI, 17%-21%) (217 of 1137) in those receiving the combination of Thalidomide, dexamethasone, and doxorubicin hydrochloride, and 13% (95% CI, 9%-16%) (45 of 351) in those receiving the combination of Thalidomide, melphalan, and prednisone, showing incidences of not less than 10% in patients receiving combination therapy with Thalidomide and other anti-neoplastic agents (*JAMA*. 2006;296:2558-2560). There is a foreign report stating that the incidence of VTE can be reduced by prophylactic administration of aspirin, warfarin sodium, or low molecular weight heparin (*Blood*. 2008;111:3968-3977).

The PMDA considers as follows:
Although no VTE occurred in the Japanese clinical study, observed changes in the levels of coagulation factors (FDP, D dimer) suggest the potential risk of VTE in Japanese patients treated with Thalidomide. Therefore, close monitoring of clinical symptoms as well as examination for blood coagulation factors (FDP, D dimer, TAT) is warranted after marketing.

In the Japanese clinical study, patients with a history of VTE were excluded. However, patients with a high risk of VTE may be treated with Thalidomide after marketing. Therefore, the PMDA asked for the applicant's view on the necessity of advising caution in the use of Thalidomide in patients with a history of VTE and on the necessity for anticoagulant therapy to prevent VTE.

The applicant responded as follows:
The Careful Administration section in the package insert will include the description "Patients with past or concurrent venous thromboembolism [Administration of this product may aggravate symptoms]." Further investigations will be needed to assess the necessity of preventive measures against VTE, such as anticoagulant therapy, concomitantly administered with Thalidomide. The necessity of advising caution in the package insert will be examined after sufficient evidence has been accumulated by collecting relevant information in Japan and overseas after marketing.

The PMDA considers as follows:
Although safety information on patients with a history of VTE is not available, there is currently no evidence that justifies contraindication of Thalidomide in these patients. Therefore, the applicant's response is acceptable. After marketing, administration of Thalidomide in combination with other anti-neoplastic agents is expected. In particular, combination of Thalidomide and steroids such as dexamethasone is reported to increase the incidence of VTE as compared with Thalidomide monotherapy (*Blood*. 2008;111:3968-3977), and thus requires special attention. Therefore, it is necessary to carefully follow patients receiving Thalidomide in combination with dexamethasone or other anti-neoplastic agents, by frequently performing examinations for blood coagulation factors. There is currently no sufficient evidence available in Japan for the usefulness of prophylactic administration of low molecular weight heparin, warfarin, aspirin, etc., against VTE caused by Thalidomide. The usefulness of methods for VTE prophylaxis should be evaluated in Japanese clinical studies, etc., as is conducted in the foreign comparative study on enoxaparin vs. aspirin vs. low-dose warfarin (*Blood*. 2007;110 [abstract 310]). Since VTE is also known to occur as an adverse reaction to oral contraceptives, it will be necessary to exercise due caution regarding

the risk of a further increase in the incidence of VTE if a contraceptive is co-administered with Thalidomide. In addition, there is a report which states that the incidence of VTE is approximately 3 times higher (28% vs. 9%) in patients treated with the Thalidomide analog lenalidomide when erythropoietin is administered in combination with dexamethasone (*JAMA*. 2006;296:2558-2560), requiring additional caution for co-administration of drugs other than anti-neoplastic agents as well.

Deliberation should be made at the Expert Discussion to reach a conclusion regarding the precautions against VTE.

4.3.B.4).(3) Tendency for lethargy/somnolence

As is evident from the fact that Thalidomide had been marketed since 1957 as a sedative and used for treating insomnia as well, one of the major adverse reactions to the drug is the tendency for lethargy/somnolence, a pharmacological action of Thalidomide (*Cancer Principles and Practice of Oncology*. 8th ed. PA, USA: Lippincott Williams & Wilkins; 2008, etc.). Although somnolence or depressed level of consciousness was not observed in the Japanese clinical study, it is necessary to continuously pay attention even after marketing to the tendency for somnolence, particularly that occurring in the day time.

4.3.B.4).(4) Orthostatic hypotension

In the Japanese clinical study, heart rate and rhythm disorders occurred in 12 subjects (32.4%) and sinus bradycardia in 6 (16.2%). Although these events may possibly have been due to autonomic nervous system disorders, dizziness was also observed in 11 subjects (29.7%). The seriousness was evaluated as Grade 2 in 2 subjects with bradycardia, and Grade 3 or higher bradycardia was not observed.

In light of a report that the incidence of bradycardia overseas is 0.12% (*Mayo Clin Proc.* 2000;75:897-901), there is a concern about the possibility of a higher incidence of orthostatic hypotension, etc., in Japanese patients. In the US package insert of a Thalidomide product with a formulation different from that of the proposed product, caution is advised against orthostatic hypotension, dizziness, and bradycardia as adverse reactions to the drug. Thus, when a drug with a negative chronotropic effect, such as a β-receptor blocker, is used for the treatment of concurrent disease, etc., it will be necessary to pay special attention, such as avoiding the administration of Thalidomide and adjusting the dose of the concomitant antihypertensive drug.

4.3.B.4).(5) Inhibition of angiogenesis

Thalidomide is suggested to inhibit angiogenesis (*Wintrobe's Clinical Hematology*. 11th ed. PA, USA: Lippincott Williams & Wilkins; 2004, *Cancer Principles and Practice of Oncology*. 8th ed. PA, USA: Lippincott Williams & Wilkins; 2008, etc.).

In the Japanese clinical study, 1 death due to gastrointestinal perforation was reported. In this subject (subject No. 32, 7[redacted] year-old man), administration of Thalidomide was discontinued on Day 8 of treatment due to aggravation of the primary disease, and the patient died of gastrointestinal perforation 17 days after discontinuation of treatment. The causal relationship to Thalidomide was judged by the investigator to be "unknown."

Bevacizumab (genetic recombination), an anti-VEGF antibody which has anti-angiogenic activity, is known to cause wound healing delayed and gastrointestinal perforation as adverse drug reactions. In the Japanese clinical study of Thalidomide, the following adverse reactions that are known to be caused by bevacizumab (genetic recombination) were observed in addition to gastrointestinal perforation: blood pressure increased in 4 subjects (10.8%, judged to be an adverse reaction in 2 subjects) and urinary protein positive in 21 subjects (56.8%, judged to be an adverse reaction in 10 subjects).

The PMDA asked for the applicant's view on the safety concern about inhibition of angiogenesis by Thalidomide and on the necessity of advising caution regarding the risk.

The applicant responded as follows:
Gastrointestinal perforation and wound healing delayed will be included in "Clinically significant adverse reactions" in the package insert to advise caution.

The PMDA considers as follows:
Cautions should be exercised against gastrointestinal perforation and wound healing delayed. Also, in addition to the potential for wound healing delayed, bone marrow depression such as neutrophil count decreased is observed. Therefore, it will be necessary to pay special attention in the post-operative use of Thalidomide.

4.3.B.4).(6) Eruption
In the Japanese clinical study, skin and appendage disorders were observed in 20 subjects (54.1%), of which major adverse events were eruption/rash in 14 (37.8%) and itchy skin in 6 (16.2%). The incidence of mild to moderate eruption was reportedly 46% in the Thalidomide monotherapy group and 43% in the group receiving combination therapy with Thalidomide and dexamethasone (*J Am Acad Dermatol.* 2003;48:548-552), from which the PMDA has confirmed that the incidence in the Japanese clinical study is not significantly different from that reported in the foreign study.

In a foreign phase II study in untreated MM patients, a toxic epidermal necrolysis case was reported (*N Engl J Med.* 2000;343:972-973). This subject received combination therapy with Thalidomide and dexamethasone, and a causal relationship to Thalidomide could not be denied. The applicant therefore noted that dexamethasone will be included in "Precautions for combined use" in the package insert of Thalidomide.

In patients treated with Thalidomide formulations different from that of the proposed product, dermatitis exfoliative was observed following Thalidomide monotherapy to treat relapsed MM, and erythema multiforme exudativum following combination therapy with Thalidomide and dexamethasone (*J Am Acad Dermatol.* 2003;48:548-552). Therefore, the PMDA considers it necessary, if eruption is noted during treatment with the proposed product, to take prompt measures including dose interruption or discontinuation and to recommend consulting a dermatologist.

4.3.B.4).(7) Constipation
In the Japanese clinical study, constipation occurred in 24 subjects (64.9%), some receiving Thalidomide at the lowest dose of 100 mg. The PMDA considers it necessary to pay attention to control of bowel movements such as by using a laxative because constipation may cause intestinal obstruction or ischaemic bowel disease, particularly in elderly patients.

4.3.B.4).(8) Hypothyroidism
In the Japanese clinical study, there were no reports of hypothyroidism. However, there is a report that the thyroid-stimulating hormone (TSH) level increased significantly, by more than 5 μIU/mL in 20% (18 of 92) of MM subjects receiving combined treatment with chemotherapy and Thalidomide, as compared with the level in 9% (7 of 82) of subjects receiving chemotherapy alone. The report also states that an increase in TSH level by more than 5 μIU/mL was observed in 22% (18 of 81) of subjects with relapsed MM after 2 to 6 months of treatment with Thalidomide (*Am J Med.* 2002;112:412-413).

The PMDA considers it necessary to perform appropriate examinations if patients complain of depression and other relevant clinical symptoms, by considering the possibility of hypothyroidism.

4.3.B.4).(9) Teratogenicity

In the Japanese clinical study, no pregnancies or deliveries were reported. Since the report of Thalidomide embryopathy (*Lancet.* 1962;151, *Lancet.* 1963;501-502), approximately 1000 victims of Thalidomide (officially acknowledged victims, 309) have been reported in Japan ("Guideline for the appropriate use of Thalidomide in the treatment of multiple myeloma," Committee on Appropriate Use of Drugs, the Japanese Society of Clinical Hematology, http://www.rinketsu.jp/ [as of July 2008]; the MHLW Project for FYs 2003 and 2004 for promotion of proper use of drugs by related academic societies). Worldwide, approximately 12,000 children born with limb malformations have been reported (*Br Med J.* 2007;334:933).

The early stage of pregnancy, the first three months in particular, is called the embryonic period when organs are formed. Taking Thalidomide during this period causes inhibition of the growth of tissues such as capillary vessels, resulting in abnormal fetal organogenesis. The drug is also secreted into seminal fluid.

Therefore, in judging the appropriateness of the approval of Thalidomide, the measures taken against teratogenicity are among the most important factors. Safety management regarding this problem is being addressed separately, as described above [see "1.2 History of development of Thalidomide"].

4.3.B.4).(10) Bone marrow depression

Cases of bone marrow depression observed in the Japanese clinical study were as shown in the table below.

	No. of subjects (%)	
	All adverse events	Adverse events of Grade 3 or more
White blood cell count decreased	17 (45.9%)	6 (16.2%)
Neutrophil count decreased	21 (56.8%)	10 (27.0%)
Lymphocyte count decreased	16 (43.2%)	5 (13.5%)
Basophil count decreased	2 (5.4%)	0 (0%)
Eosinophil count decreased	5 (13.5%)	0 (0%)
Monocyte count decreased	5 (13.5%)	0 (0%)
Red blood cell count decreased	4 (10.8%)	0 (0%)
Anaemia	1 (2.7%)	1 (2.7%)
Haemoglobin decreased	10 (27.0%)	4 (10.8%)
Haematocrit decreased	3 (8.1%)	0 (0%)
Platelet count decreased	11 (29.7%)	0 (0%)

In the Japanese clinical study, administration of Thalidomide was discontinued because of bone marrow depression in patients, as listed in the following table.

List of subjects in whom discontinuation was due to bone marrow depression
(Japanese clinical study)

Age	Gender	Dose (mg)	Adverse event that led to discontinuation	Grade	Time of onset (Day)	Duration (days)	Outcome
6[redacted]	Female	100	Haemoglobin decreased	3	8	56	Not recovered
6[redacted]	Female	100	White blood cell count decreased	3	7	23	Recovered
7[redacted]	Male	100	Neutrophil count decreased	3	29	8	Recovered
7[redacted]	Female	100	White blood cell count decreased, haemoglobin decreased	3, 3	8, 8	3, 22	Recovered
4[redacted]	Female	200	Neutrophil count decreased	3	85	43	Improved

The PMDA considers as follows:

Neutrophil count decreased was observed in approximately 60% of subjects, and the severity was Grade 3 or more in approximately 30% of subjects. Given that MM is accompanied by decreased immune function and that Thalidomide is intended to be used in patients with relapsed or refractory MM with history of treatment with multiple anti-neoplastic agents, special attention should be paid to infection while patients are treated with Thalidomide.

4.3.B.4).(11) Cautions in administering Thalidomide to patients with human immunodeficiency virus (HIV) infection

In a foreign clinical study in patients with HIV infection, increased HIV RNA level was observed in 16 of 29 subjects at 4 weeks after treatment with Thalidomide (median change in HIV RNA: Thalidomide group, 0.42 $\log_{10}$ copies HIV RNA/mL; placebo group, 0.05 $\log_{10}$ copies HIV RNA/mL) (*N Engl J Med.* 1997;336:1487-1493). Although the clinical significance of this finding is unclear, an increased HIV RNA level is a phenomenon counteracting the treatment, given that the primary objective of antiviral therapy for patients with HIV infection is to suppress viraemia ("Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents," January 29, 2008 edition by the US Department of Health and Human Services). Therefore, in

using Thalidomide in patients with HIV infection, it is necessary to pay attention to, such as frequently measuring the HIV RNA level. Also, there are reports that administration of Thalidomide aggravated infections by other viruses such as hepatitis B and herpes (*J Clin Microbiol.* 2002;40:2302-2304, etc.). Therefore, it will be necessary to collect information on HIV and other viral infections and to assure prompt release of such new information.

4.3.B.4).(12) Long-term treatment

As of November 30, 2006, the treatment status (results based on the monitoring record) in the ongoing long-term treatment study is shown in the table below. In total, 20 subjects proceeded to the long-term treatment study, of whom 14 are continuing, while 6 have discontinued, to receive treatment with Thalidomide. No new serious adverse drug reactions have been reported.

Current status	Dose (mg/day)	Percent changes in M protein level	Note
Ongoing at Week 104	100	-24.1%	
Ongoing at Week 104	100	-19.5%	
Ongoing at Week 104	100	-94.9%	
Discontinued at Week 71	200	-7.8%	Discontinuation of treatment due to an adverse drug reaction (VTE in lower right limb. Evaluated as non-serious because of the lack of subjective symptoms. This has been reported to each study site.)
Discontinued at Week 31	100	-70.9%	Discontinuation of treatment due to aggravation of the primary disease (Death, unrelated to Thalidomide)
Ongoing at Week 96	100	+1791.8%	Ongoing at request of the subject. BJ-type MM. The percent increase is large because of very low baseline M protein level.
Ongoing at Week 96	100	-1.2%	
Ongoing at Week 96	100	+18.9%	
Ongoing at Week 104	100	-67.4%	
Ongoing at Week 100	100	-67.0%	
Discontinued at Week 116	100	-4.0%	Discontinuation of treatment due to aggravation of the primary disease (IgG increased, unrelated to Thalidomide)
Ongoing at Week 96	100	-35.1%	
Ongoing at Week 104	100	-78.6%	
Discontinued at Week 92	100	-55.6%	Discontinuation of treatment due to aggravation of the primary disease (Extramedullary mass formation, unrelated to Thalidomide)
Ongoing at Week 104	300	-44.2%	
Ongoing at Week 100	100	-12.6%	
Ongoing at Week 104	400	-52.2%	
Discontinued at Week 52	400	+41.5%	Discontinuation of treatment at the request of the subject (treatment method changed)
Discontinued at Week 78	200	-19.2%	Discontinuation of treatment due to change to a different treatment method
Ongoing at Week 108	100	-69.0%	

The PMDA considers as follows:

Currently, safety information on only up to 16-week treatment has been obtained from the Japanese clinical study. Also, only limited information has been available from subjects who proceeded to the long-term treatment over 16 weeks. Therefore, it will be necessary to collect safety information in patients treated for a long-term period after marketing [see "4.3.B.9) Matters to be investigated after marketing"].

4.3.B.5) Clinical positioning

The cumulative incidence of MM in Japan in people 0 to 74 years of age (in 1999) was 0.17% in men and 0.14% in women (The Research Group for Population-based Cancer Registration in Japan. *Jpn J Clin Oncol.* 2004;34:352-356). The incidence by age shows that the disease is prevalent mainly in adults 40 years of age or older, particularly in the elderly, 60 to 70 years of age, and is rare in young people 30 years or under (*Miwa's Hematology.* 3rd ed. Tokyo: Bunkodo; 2006). There were an estimated 3655 patients with MM across Japan in 1999, accounting for 0.7% of all patients with malignant neoplasms and 15% of patients with hematopoietic tumors. The incidence of MM has remained roughly unchanged since 1990. MM is a disease with a poor prognosis with a death to new-onset ratio of 3:4 and median survival time of approximately 33 months (*Mayo Clin Proc.* 2003;78:21-33), with no established effective treatment method available. Thus, it is one of the diseases for which development of new therapeutic drugs is eagerly awaited.

The PMDA has confirmed that, according to the NCCN Clinical Practice Guidelines in Oncology (version 2, 2008; NCCN Guideline) (http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf [as of June 2008]) which are used as a reference by Japanese and overseas clinical oncologists, recommended remission induction therapies include Thalidomide/dexamethasone (Category 2A, based on lower-level evidence including clinical experience and uniform consensus) and bortezomib/Thalidomide/dexamethasone (Category 2B, based on lower-level evidence including clinical experience and non-uniform consensus [but no major disagreement]) for patients who are candidates for hematopoietic stem cell transplantation; melphalan/prednisone/Thalidomide (Category 1, based on high-level evidence and uniform consensus) and Thalidomide/dexamethasone (Category 2A) for patients who are not candidates for hematopoietic stem cell transplantation; and Thalidomide monotherapy, Thalidomide/dexamethasone, and DT-PACE therapy (dexamethasone/Thalidomide/cisplatin/doxorubicin hydrochloride/cyclophosphamide/etoposide) (Category 2A) as rescue therapies.

Harrison's Principles of Internal Medicine. 17th edition (USA: McGraw-Hill; 2008), a standard textbook of internal medicine, recommends the following treatments as standard therapies: melphalan/prednisone (MP therapy) as the initial treatment in patients who are not candidates for hematopoietic stem cell transplantation, and melphalan/prednisone/Thalidomide as the initial treatment in patients age 65 years or older. The PMDA has also confirmed the descriptions in this book regarding the use of Thalidomide as a maintenance therapy after hematopoietic stem cell transplantation is currently undergoing evaluation and that Thalidomide is effective for relapsed or refractory MM. *Wintrobe's Clinical Hematology.* 11th edition (PA, USA: Lippincott Williams & Wilkins; 2004), a standard textbook of hematology, recommends Thalidomide as one of the standard therapeutic agents for MM ("Thalidomide is now considered a standard therapy for multiple myeloma."). *Cancer Principles and Practice of Oncology.* 8th edition (PA, USA: Lippincott Williams & Wilkins; 2008), a standard textbook of clinical oncology, states that Thalidomide has been confirmed to be effective for relapsed or refractory MM and that the drug is effective when used as a combination therapy in the initial treatment as well. *Hematology.* 2007 (The American Society of Hematology Education Program Book) recommends Thalidomide along with bortezomib and lenalidomide as a therapeutic drug for relapsed or refractory MM, and describes such examples based on publications, including Thalidomide monotherapy (*Blood.* 2001;98:492-494), Thalidomide/dexamethasone (*Hematol J.* 2004;5:318-324), and Thalidomide/cyclophosphamide/dexamethasone (*Hematol J.* 2004;5:112-117). In *Miwa's Hematology.* 3rd edition (Tokyo: Bunkodo; 2006), a standard textbook of hematology in Japan, a description of Thalidomide appears in the section on investigative treatments, and states that the drug is effective in approximately one third of patients with refractory MM and that the daily dose of 100 to 200 mg can be used even in elderly patients, citing publications (*Leuk Lymphoma.* 2003;44:1943-1946, *Leuk Lymphoma.* 2003;44:989-991, *Mayo Clin Proc.* 2003;78:34-39).

The PMDA considers the clinical positioning of Thalidomide in the treatment of MM, as follows:
The PMDA has confirmed that, in the Japanese clinical study involving patients with MM relapsing after hematopoietic stem cell transplantation or with chemotherapy-resistant MM (primary cases treated with not more than 3 regimens, including steroid monotherapy, but excluding radiation therapy), the proposed product reduced the M protein level, and that the product is therefore expected to be useful when administered appropriately as a salvage therapy for relapsed or refractory MM, as judged by the description of Thalidomide in books in Japan and overseas.

MM is not considered to be curable by conventional therapies (NCCN Guideline). In most patients, the disease relapses after the initial treatment (*Mayo Clin Proc.* 1994;69:781-786), with the median survival time in patients with relapsed or refractory MM being 6 to 9 months (*Hematology Am Soc Hematol Educ Program.* 2007). Therefore, the PMDA understands that drug therapy for relapsed or refractory MM is performed with an expectation of prolongation of survival time. In contrast, only changes in serum M protein level were used as the index for evaluating efficacy in the Japanese clinical study.

Based on the above, the PMDA has judged that the clinical positioning of the proposed product in Japan is limited, at present, to treatment of patients with MM relapsing after hematopoietic stem cell transplantation or chemotherapy-resistant MM in whom other therapies are ineffective or cannot be performed. However, since no information is currently available on the overall survival of Japanese patients treated with the proposed product, it will be necessary to collect information on the overall survival benefit of Thalidomide and long-term safety of the proposed product, including those obtained from publications, after marketing, and to promptly release the analysis results after a certain period.

Deliberation should be made at the Expert Discussion to reach a final conclusion regarding the above judgment of the PMDA.

4.3.B.6) Indications
As a result of the review described below, the PMDA has concluded that it is appropriate that the indications for Thalidomide be "relapsed or refractory multiple myeloma" based on the evaluation data submitted with the present application.

4.3.B.6).(1) Relapsed or refractory MM
The Japanese clinical study, the results of which have been submitted as evaluation data, was conducted in patients with relapsed or chemotherapy-resistant MM. As described under "4.3.B.5) Clinical positioning," the PMDA considers Thalidomide monotherapy to be positioned as one of the salvage therapies for relapsed or refractory MM, based on the results of the Japanese clinical study and on the descriptions in books in Japan and overseas.

4.3.B.6).(2) Untreated MM
In the US, Thalidomide is approved for combination therapy with dexamethasone in patients with newly diagnosed MM.

The PMDA asked the applicant about the future development plan for the proposed product, which has a formulation different from that of Thalidomide products marketed in foreign countries, for untreated MM.

The applicant responded as follows:
The applicant has no specific development plan for untreated MM. When the proper use and safety management system have become widely established after marketing approval, and if the proposed product is used off-label in untreated MM patients, a clinical study will be conducted to obtain an

additional indication for initial treatment.

The PMDA considers as follows:
Since the following investigations have been performed using Thalidomide products with formulations different from that of the proposed product, it is hoped that studies of the proposed product for untreated MM in Japanese patients will be conducted. Also, it is desirable that the combination therapy with the proposed product and dexamethasone be investigated in Japanese patients who are candidates for hematopoietic stem cell transplantation as a remission induction therapy, as recommended by the NCCN Guideline (Category 2A). Thalidomide has been reported to be effective as the initial treatment for smoldering myeloma as well (*Leukemia*. 2003;17:775-779). However, the clinical significance of aggressive treatment for smoldering myeloma has not been established (NCCN Guideline), and thus remains an issue to be addressed in the future.

In a double-blind, randomized phase III study comparing Thalidomide/dexamethasone combination therapy versus dexamethasone monotherapy in untreated MM subjects, the response rate (ECOG criteria) was 63% vs. 46%, and time to progression (TTP) was 22.6 months vs. 6.5 months, showing a significant superiority of Thalidomide/dexamethasone (*J Clin Oncol*. 2008;26:2171-2177). In this study, however, Grade 3 or more severe non-hematological toxicity occurred in 80% (186 of 234) and 64% (149 of 232) of subjects, respectively, and Grade 4 or more severe toxicity occurred in 30% (71 of 234) and 23% (53 of 232), respectively, showing a higher incidence of non-hematological toxicity in the combination therapy group. In particular, Grade 3 or more severe VTE was observed more frequently in the Thalidomide/dexamethasone group (11.5% [27 of 234] vs. 1.7% [4 of 232]). Therefore, the risk-benefit of combination of Thalidomide and dexamethasone will be an issue to be addressed in the future. Besides Thalidomide/dexamethasone combination therapy, the add-on effect of Thalidomide to vincristine/dexamethasone/pegylated liposomal doxorubicin (not approved for MM in Japan) (*Ann Oncol*. 2007:18:1369-1375) and that to melphalan/prednisone (*Blood*. 2007;110:32a [abstract 78]) have been investigated in comparative studies. In addition to these combination therapies in untreated MM patients, investigations have been conducted on the use of Thalidomide as a pretreatment before autologous transplantation combined with high-dose chemotherapy and as a remission maintenance therapy (*Blood*. 2008;111:1805-1810, *Lancet*. 2007;370:1209-1218, *N Engl J Med*. 2006;354:2079-2080, *Lancet*. 2006;367:825-831, *Bone Marrow Transplant*. 2005;36:193-198, *Blood*. 2005;106:35-39, *J Clin Oncol*. 2003;21:16-19, *J Clin Oncol*. 2002;20:4319, etc.).

4.3.B.6).(3) MM not investigated in Japanese clinical study
Regarding the use of the proposed product in patients with non-secretory myeloma, who had been excluded from the Japanese clinical study, the applicant explained as follows:
The apparent symptoms of MM are caused mainly by growth of neoplastic plasma cells in the bone marrow, and non-secretory MM patients with no detectable M protein are treated in a manner similar to that for other MM patients (*Myeloma Today*. 2000;4:2). Also, according to the *Guideline for the treatment of multiple myeloma* (Japanese Society of Myeloma, ed. Bunkodo), non-secretory MM is not differentiated from other types of MM in treatment. Based on these references, it is appropriate to include non-secretory multiple myeloma among the indications for the proposed product.

The PMDA considers as follows:
Since the efficacy of Thalidomide in non-secretory multiple myeloma was not investigated in the Japanese clinical study, the applicant's response is not considered appropriate. However, non-secretory multiple myeloma is an extremely rare disease, and it is therefore difficult to conduct a study to evaluate the efficacy of Thalidomide in patients with this disease. In addition, it is very unlikely that safety concerns unique to non-secretory multiple myeloma will arise from use

of the proposed product. Therefore, it is concluded that non-secretory multiple myeloma, a type of plasma cell neoplasm, need not be excluded from the indications for the proposed product.

Thalidomide has also been reported to be effective in relapsed or refractory plasma cell leukemia (*Leuk Lymphoma.* 2002;43:351-354, *Acta Haematol.* 2003;109:153-155, etc.). In light of the fact that plasma cell leukemia is extremely rare as is the case with non-secretory multiple myeloma, and that the disease has a poor prognosis with a median survival time of 2 to 7 months (*Leuk Lymphoma.* 2007;48:5-6), it is judged that the disease need not be excluded from the indications for the proposed product. However, since there is a report stating that Thalidomide monotherapy does not improve the prognosis of plasma cell leukemia (*Leuk Lymphoma.* 2007;48:180-182), it will be necessary to collect information after marketing and to assess the results after a certain period of time.

4.3.B.7) Dosage and administration

The applicant proposed the dosage and administration as follows: "The usual adult dosage for oral use is 100 mg of Thalidomide once daily before bedtime. The dosage may be increased or decreased, according to the patient's age and symptoms, up to a maximum of 400 mg per day."

The PMDA asked the applicant the reason for selecting, as a dose escalation method in the Japanese clinical study, a dose titration design in which the "level of response" at each evaluation time point, Weeks 4, 8, and 12, was used as the criterion for the dose increase.

The applicant responded as follows:
Administration at a single fixed dose (200 mg) was initially planned in the Japanese clinical study. But the dose titration was eventually selected because patients with disease aggravation would need salvage therapy, and it should be started from 100 mg to ensure safety.

The PMDA considers as follows:
In the dose titration design set by the applicant, the dose increase had to be decided based on the "level of response" at each evaluation time point (Weeks 4, 8, and 12), and the criteria for dose reduction and for dose re-escalation had to be taken into account at the same time. It appears therefore that the dosage and administration set for the study were very complicated. In fact, in this study, the dose was reduced in several patients who did not meet the dose reduction criteria stipulated in the protocol. This study, which was positioned as an exploratory study, was not designed to allow determination of the recommended dosage and administration of Thalidomide. In addition, dose reduction was performed in violation of the protocol. Therefore, no clear conclusion was obtained from the submitted data of the Japanese clinical study for the details of the dosage and administration of the proposed product, such as the appropriate dose and criteria for dose increase or decrease, in Japanese patients.

The PMDA considers dosage and administration as follows:
Although Thalidomide is effective at doses not less than 50 to 100 mg/day overseas, no optimal dosage and administration have yet been established (*Lancet.* 2004;363:875-887). *Wintrobe's Clinical Hematology.* 11th edition (PA, USA: Lippincott Williams & Wilkins; 2004) also states that the correlation between the efficacy of Thalidomide and its dose is unknown ("The role of dose intensity in Thalidomide effectiveness is unclear.") based on publications (*Br J Haematol.* 2000;111:986, *Haematologica.* 2000;85:1111-1112). There are also reports which suggest a high response rate and prolongation of survival in high risk patients treated with a high daily dose (≥ 600 mg) (*Blood.* 2001;98:492-494) or effectiveness of a low daily dose (100 mg) (*Haematologica.* 2000;85:1111-1112). Foreign clinical studies have confirmed a daily dose of 50 to 800 mg to be effective in reducing M protein level in MM patients [see 4.3.B.3).(1) Serum M protein-reducing effect"] and investigated the efficacy of Thalidomide at doses below 100 mg and above 400 mg, ranges not covered by the Japanese clinical study. Both in the dosage and the administration of the

proposed product in Japan and in the approved doses of Thalidomide overseas, although the initial dose is set, no fixed optimal dose has yet been determined.

Thus, details of the relationship between the dose and efficacy of Thalidomide have not been clarified in either Japanese clinical studies or publications. Also, the safety of Thalidomide at high doses exceeding the upper limit of the dose increase planned in the Japanese clinical study (400 mg/day at maximum) has not been investigated. Therefore, it was judged appropriate to set the dosage and administration at 100 to 400 mg once daily, the regimen investigated in the Japanese clinical study.

The details of the review by the PMDA are described below.

4.3.B.7).(1) Dosage and administration and dose adjustment rule
In the Japanese clinical study, treatment was started at the initial dose of 100 mg administered before bedtime, followed by a dose increase by 100 mg each at Weeks 5, 9, and 13 after starting treatment. If the subject showed MR or better response at Week 4, 8, or 12, the existing dose was to be maintained. When Grade 2 non-hematological toxicity or Grade 3 hematological toxicity was observed, the dose was to be decreased if the existing dose was 200 mg or higher, and the treatment was to be discontinued if 100 mg was being used. If no recovery from, or improvement of, symptoms was observed 1 week after dose reduction, the dose was to be further reduced. If the "level of response" was rated as "no change (NC)" during the treatment at a maintained dose, the dose was to be increased by 100 mg each at Weeks 8 and 12.

The following table lists subjects with protocol violations, as reported by the applicant.

Subjects with protocol violations and reasons for the violations

Subject No.	Reason
8	Treatment not discontinued at the occurrence of Grade 3 hematological toxicity (lymphocyte count decreased)
	Dose not reduced by 100 mg at the occurrence of Grade 3 hematological toxicity (lymphocyte count decreased)
12	Treatment not discontinued at the occurrence of Grade 3 hematological toxicity (white blood cell count decreased, lymphocyte count decreased, neutrophil count decreased, haemoglobin decreased)
13	Treatment not discontinued at the occurrence of Grade 3 hematological toxicity (white blood cell count decreased)
	Treatment not discontinued at the occurrence of Grade 3 hematological toxicity (neutrophil count decreased)
20	Treatment not discontinued at the occurrence of Grade 3 hematological toxicity (white blood cell count decreased, neutrophil count decreased)
	Treatment not discontinued at the occurrence of Grade 3 hematological toxicity (neutrophil count decreased)
22	Treatment not discontinued at the occurrence of Grade 3 hematological toxicity (neutrophil count decreased)
27	Treatment not discontinued at the occurrence of Grade 3 hematological toxicity (haemoglobin decreased, white blood cell count decreased, neutrophil count decreased)
	Treatment not discontinued at the occurrence of Grade 3 hematological toxicity (haemoglobin decreased)
38	Treatment not discontinued at the occurrence of Grade 2 non-hematological toxicity (constipation)
	Treatment not discontinued at the occurrence of Grade 2 non-hematological toxicity (general malaise)
40	Treatment not discontinued at the occurrence of Grade 2 non-hematological toxicity (creatinine increased)
	Dose not reduced by 100 mg at the occurrence of Grade 3 hematological toxicity (lymphocyte count decreased)
41	Dose not reduced by 100 mg at the occurrence of Grade 3 hematological toxicity (neutrophil count decreased)
	Treatment not discontinued at the occurrence of Grade 2 non-hematological toxicity (proteinuria)

The dose adjustment rule stipulated in the protocol did not specify a causal relationship of adverse events to the investigational drug, which is explained by the applicant as follows:

a. The criteria for dose reduction and for discontinuation stipulated in the protocol used the

terms "non-hematological toxicity" and "hematological toxicity," thereby clearly differentiating these events from adverse events.

b. "Non-hematological toxicity" and "hematological toxicity" are terms used in the treatment of multiple myeloma. These episodes are not to be regarded as meeting the criteria for discontinuation or for dose reduction, unless they correspond to "adverse drug reactions" (adverse events other than those judged as "unrelated").

Upon examination of all adverse events including those other than adverse drug reactions, the PMDA found some subjects with protocol violations as to dose adjustment in addition to those presented by the applicant (see table below).

Subject No.	Reason
2	Treatment discontinued because of alleged disease aggravation, but "level of response" and final evaluation were both NC.
4	NC at Week 5, but 100 mg/day maintained without dose increase.
5	MR at Week 5, but dose increased to 200 mg/day.
6	Dose reduced from 300 mg/day to 200 mg/day because of Grade 2 white blood cell count decreased.
7	Dose reduced from 200 mg/day to 100 mg/day because of Grade 1 queasy.
10	"Level of response" was NC but dose maintained at 200 mg/day without increase as required. Treatment withdrawn (due to patient's choice) because of queasy.
17	Treatment (200 mg/day) withdrawn twice due to patient's choice.
25	Dose reduced from 200 mg/day to 100 mg/day because of Grade 1 sleepiness.
37	Dose increased from 100 mg/day to 200 mg/day deviating from the discontinuation criteria.
40	Dose maintained at 200 mg/day despite Grade 3 lymphocyte count decreased. Dose reduced to 100 mg/day because of Grade 1 rash.

The final dose in the Japanese clinical study was 100 mg in 20 subjects (58.8%), 200 mg in 7 (20.6%), 300 mg in 2 (5.9%), and 400 mg in 5 (14.7%). Although it is difficult to determine the recommended dosage and administration from the results of the Japanese clinical study, given the study treatment experience of daily administration of 100 to 400 mg, adjusting the daily dose within the range from 100 to 400 mg is unavoidable, on condition that careful attention is paid to each patient's condition. However, there are publications reporting the efficacy of doses below 100 mg/day or above 400 mg/day [see 4.3.B.3).(1) Serum M protein-reducing effect"]. Therefore, the PMDA considers it necessary to develop a lower-dose formulation and, in future, to evaluate efficacy at doses below 100 mg/day and above 400 mg in Japanese patients.

Deliberation should be made at the Expert Discussion to reach a final conclusion regarding the above view of the PMDA.

4.3.B.7).(2) Combination with other anti-neoplastic agents

In the Japanese clinical study data submitted with the present application, Thalidomide was administered as monotherapy, and no evaluation data was submitted on combination therapy with the proposed product and other anti-neoplastic agents.

Since combination therapy with the proposed product and other anti-neoplastic agents was not investigated in the submitted data, the PMDA does not recommend, at present, administration of the proposed product in combination with other anti-neoplastic agents. As information on combination therapy, there are reports of *in vitro* synergistic effects between Thalidomide and dexamethasone in the inhibition of myeloma cell growth (*Cancer Principles and Practice of Oncology*. 8th ed. PA, USA: Lippincott Williams & Wilkins; 2008, *Wintrobe's Clinical Hematology*. 11th ed. PA, USA: Lippincott Williams & Wilkins; 2004) and of favorable results obtained by combination of Thalidomide and dexamethasone in relapsed or refractory MM in

foreign clinical studies (see table below).

Thalidomide/dexamethasone combination therapy in patients with relapsed or refractory MM

Doses (Thalidomide + dexamethasone)	No. of patients	Responders (%)	Reference
100 mg/day + 40 mg (Days 1-4)	120	62 (51.6)	*Hematol J.* 2004;5:318
200-400 mg/day + 20 mg/m^2 (Days 1-4; Days 9-12 and Days 17-20 added only during the first 1 month)	44	24 (54.5)	*Ann Oncol.* 2001;12:991
100 mg/day + 40 mg (Days 1-4)	77	32 (41.6)	*Haematologica.* 2001;86:399-403

Regarding information on administration of Thalidomide in combination with drugs other than dexamethasone, there are reports of a phase II study of combination therapy with Thalidomide and interferon in patients with relapsed or refractory MM (*Blood.* 2003;102:69-77) and of a randomized study comparing MP therapy (melphalan/prednisone) and MP therapy/Thalidomide in untreated elderly patients with MM (*Lancet.* 2006;367:825-831). Also, in the 2007 Annual Meeting of the American Society of Clinical Oncology (ASCO), results of the combination of Thalidomide and MP therapy in untreated MM patients (*J Clin Oncol.* 2007;25(18 suppl):441s [abstract 8001]) and results of the combination of Thalidomide, low-dose dexamethasone, and zoledronic acid hydrate (*J Clin Oncol.* 2007;25(18 suppl):702s [abstract 18506]) were reported, showing favorable results of Thalidomide in combination with other anti-neoplastic agents regardless of patients' treatment histories.

The applicant explained as follows:
Dexamethasone and other anti-neoplastic agents may be administered in combination with Thalidomide based on the "Guideline for the appropriate use of Thalidomide in the treatment of multiple myeloma" (Japanese Society of Clinical Hematology, the MHLW Project for FYs 2003 and 2004 for promotion of proper use of drugs by related academic societies, 2003), the study report on the actual use of Thalidomide in member institutions of the Japanese Society of Myeloma, and publications. Therefore, caution will be advised in the package insert regarding the risk of VTE in the combination with doxorubicin hydrochloride, possible increased risk of peripheral nerve disorders in the combination with vincristine sulfate, the risk of toxic epidermal necrolysis in the combination with dexamethasone, and the risk of renal insufficiency in the combination with zoledronic acid hydrate.

The PMDA considers as follows:
Information on administration of Thalidomide in combination with other anti-neoplastic agents is limited to that of publications, and raising caution about the above 4 drugs alone, as explained by the applicant, is insufficient. Upon marketing of the proposed product, it is necessary to provide information to medical professionals with the package insert, etc., regarding the fact that there is no information available on combination use of the proposed product with other anti-neoplastic agents.

4.3.B.8) Contraception
In the Japanese clinical study, subjects for whom contraception was required (male subjects having female partners with child-bearing potential and female subjects with child-bearing potential) and their partners were required to take specified contraceptive measures (at least 1 method from among hormonal contraceptives, intrauterine device (IUD), and tubal ligation for female subjects with child-bearing potential; latex condoms for male subjects).

The applicant explained as follows:
In the Japanese clinical study, there were no pregnancies. All 15 subjects and their partners for whom contraception was required were confirmed to have contraceptive measures. The contraceptive methods used were an oral contraceptive in 1 subject, abstinence during the study period (including no possibility of having sexual intercourse) in 8, and unknown in 6.

The PMDA considers as follows:
A prerequisite to approval of the proposed product is to ensure appropriate contraceptive measures and procedures including methods of confirming patient compliance. This issue is being discussed separately as one of the most critical issues in safety management.

4.3.B.9) Matters to be investigated after marketing

4.3.B.9).(1) Post-marketing surveillance

The applicant plans to conduct the following investigation as post-marketing surveillance. As reasons for setting the surveillance period and sample size, the applicant explained that it would be difficult to accumulate the necessary number of patients due to the low possibility of combination with other therapies and the limited number of patients given the indications for the proposed product ("Multiple myeloma [to be used only when conventional treatment is not sufficiently effective]).

Objectives:	a. To evaluate efficacy and safety when imported Thalidomide products are switched to the proposed product b. To collect information on serious adverse drug reactions c. To evaluate long-term safety
Survey method:	All-case investigation
Surveillance period:	1 year 6 months after marketing
Sample size:	a. 700 patients registered in 400 institutions during 1 year after marketing (evaluation period, 4 weeks) b. Number of patients registered at 100 institutions during 1 year after marketing or 200 patients (evaluation period, 16 weeks) c. Among patients described in (b) above, those receiving continued administration after 16 weeks (maximum follow-up period, 2 years)
Major surveillance item:	Effects of combination with other drugs on safety

The PMDA asked the applicant the reason for setting the evaluation period at 16 weeks, to which the applicant explained that the evaluation period was set based on the fact that statistically significant decreases in M protein level induced by Thalidomide were observed within 4 weeks after starting treatment in all Japanese responders (*Jpn J Cancer Res.* 2002;93:1029-1036).

The PMDA considers the post-marketing surveillance of the proposed product, as follows:
Given that adverse events associated with Thalidomide are observed even after 16 weeks of treatment, that long-term safety information on the proposed product is very limited, and that the studies cited by the applicant were conducted using Thalidomide products with formulations different from that of the proposed product, the proposed evaluation period lacks sufficient evidence. It is appropriate that the evaluation period cover the entire treatment period, during which long-term safety information should be also collected.

As regards the sample size, no specific objective of the surveillance has been presented. It is inappropriate to investigate all patients without any specific objectives. However, considering that a wide array of information must be collected after marketing, although some information is available from the submitted clinical study data, it is necessary to include all patients in the surveillance within a certain period after marketing. Data from the post-marketing surveillance should, as appropriate, be subjected to interim analysis to obtain necessary information, and be used to revise the surveillance protocol. Also, it will be necessary to promptly provide appropriate information to medical professionals through communication channels including the applicant's website.

4.3.B.9).(2) Post-marketing clinical study

As described above, the PMDA has confirmed that the proposed product has reduced the tumor burden (M protein-reducing effect) in patients with relapsed or refractory MM, whereas whether the product prolongs survival or not has not been investigated. In the second-line treatment of MM, prolonging time to relapse or recurrence is of clinical significance. Therefore, it will be necessary to investigate the effects on TTP, progression-free survival (PFS), overall survival (OS), etc.

The PMDA asked the applicant about the plan for post-marketing investigation of the effects of the proposed product on OS, etc.

The applicant responded as follows:

A multi-center, randomized, open-label post-marketing clinical study of the proposed product with a central registration system is currently planned in patients with relapsed or refractory MM (target number of patients, 180; 90 per group), setting TTP, PFS, and OS as primary endpoints, and using high-dose dexamethasone, which is widely used for MM treatment in clinical practice in Japan and overseas, as a control.

The PMDA considers as follows:

The answers presented by the applicant are inappropriate in that as many as 3 primary endpoints have been set, that no concrete plan for conduct of the study has been established, and that the applicant's view on the feasibility of the study is not provided. Thus, it is impossible to judge the appropriateness of the planned post-marketing clinical study. Considering that there were protocol violations in some subjects in the clinical study as presented in the present application, the PMDA has a concern about whether or not it is possible to conduct the clinical study smoothly as planned by the applicant. In addition, there are many issues that must be investigated, including the effect of the proposed product on the OS of patients with relapsed or refractory MM, the usefulness of the proposed product in untreated MM patients as the first-line treatment, and the usefulness of the proposed product in combination with other anti-neoplastic agents. Therefore, it is necessary first to analyze the information obtained from the post-marketing surveillance, etc., and then to consider the clinical study plan. Deliberation should be made at the Expert Discussion to reach a final conclusion regarding handling of the post-marketing clinical study, including the issues described above.

III. Results of Compliance Review on the Application Document and PMDA's Conclusion

1) The PMDA's conclusion regarding the results of document compliance review

A document compliance review was conducted in accordance with the provisions of the Pharmaceutical Affairs Law for the documents appended to the NDA application form. As a result, although cases of failure of the principal investigator to affix the name and seal on case report forms, of noncompliance with the administration method or treatment duration, and of missing follow-up of adverse events were observed, there were no major problems. Therefore, it was concluded that a regulatory review can be conducted based on the submitted data.

2) The PMDA's conclusion regarding the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Law for the documents appended to the NDA application form (CTD 5.3.5-1). As a result, the following cases were noted at some study sites: protocol violations (inclusion of patients who met the exclusion criteria, failure to perform some laboratory tests, noncompliance with criteria for discontinuation and for dose escalation), suggesting that the sponsor did not appropriately monitor activities in these cases in accordance with the standard operating procedures. However, as there were no major problems, the PMDA concluded that a regulatory review can be conducted based on the application dossier submitted.

IV. Overall Evaluation

Based on the above, the PMDA considers the appropriateness of approving the proposed product in Japan, as follows:

In the present approval application, the only data submitted as results of non-clinical studies was reference data, which made evaluation extremely difficult. Since the bioequivalence of the proposed product and the Thalidomide products used in foreign clinical studies has not been investigated in humans, the foreign clinical data (including pharmacokinetic studies) cited from publications and submitted in the present application should be handled only as reference data for the pharmacokinetics, efficacy, and safety of the proposed product, although the submitted data was obtained from the identical active ingredient.

The submitted data from the Japanese clinical study contains some information on the proposed dosage regimen but is insufficient for determining the appropriate method for administration (dosage and administration), coupled with several protocol violations in the present study. Although a decreased serum M protein level, which was used as the pharmacodynamic index, has been confirmed, suggesting the efficacy of the proposed product in treating MM, further studies will be needed to determine whether the product prolongs survival. In addition, further information should be accumulated to evaluate the safety of long-term treatment with the proposed product.

Thus, the PMDA considers the results of the Japanese clinical study submitted as the evaluation data to be insufficient for evaluating the efficacy, safety, or dosage regimen.

This notwithstanding, the PMDA presented the following points.

a. As is evident from the fact that Thalidomide is designated as an orphan drug, it should be difficult to accumulate further data in clinical studies in Japan.
b. The Japanese clinical study showed that treatment with Thalidomide reduced M protein level in some subjects, raising the expectation of efficacy.
c. Except for the potential risk of teratogenicity, Thalidomide is tolerable up to 400 mg/day, taking into account the seriousness of the disease, as shown by the results of the Japanese clinical study. It is expected that adverse reactions to Thalidomide can be managed by physicians with knowledge and experience in cancer chemotherapy at medical institutions where adequate facilities for the treatment of emergencies are available.
d. There are many patients who use privately-imported Thalidomide products.

On the basis of comprehensive evaluation of the above issues, the PMDA has concluded that the proposed product can be approved at the current status, on the premise that the safety management which is discussed separately [see “1.2 History of development of Thalidomide”] is appropriately performed, and that all-case investigation and clinical study, etc., after marketing should be performed to accumulate information on the safety and efficacy of the proposed product.

Deliberation should be made at the Expert Discussion while focusing on the following issues, based on which the appropriateness of approving the proposed product will be decided.

- Efficacy
- Safety
- Indications and clinical positioning
- Dosage and administration
- Matters to be investigated after marketing

Review Report (2)

August 11, 2008

I. Product Submitted for Registration

[Brand name] Thaled Capsule 100
[Non-proprietary name] Thalidomide
[Applicant] Fujimoto Pharmaceutical Corporation
[Date of application] August 8, 2006

II. Content of the Review

The Pharmaceuticals and Medical Devices Agency (PMDA) sought the expert advisors' opinions based on the Review Report (1). Discussions with the expert advisors are outlined below.

All expert advisors have declared that they did not come under Section 1 or 2 (1) of "Immediate measures against the problem of conflict of interests involving an outside advisors of the Pharmaceuticals and Medical Devices Agency" dated May 8, 2007, regarding the proposed product.

1) Data from foreign clinical studies

Overseas, although no clinical development of the proposed product has been conducted, several drug products containing Thalidomide are commercially available. In the present approval application, publications reporting the results of clinical studies that were conducted using Thalidomide products approved overseas (foreign-marketed products) have been submitted as reference data.

Results of the comparison of dissolution profiles between the proposed product and foreign-marketed products have been reported by Japanese investigators at academic meetings [see the Review Report (1) "4.1 Biopharmaceutical data"], whereas no bioequivalence study comparing the proposed product and foreign-marketed products has been conducted.

The PMDA considers as follows:
The equivalence of dissolution behavior does not necessarily mean bioequivalence. Since bioequivalence between the proposed product and foreign-marketed products is thus unclear, there is no assurance that the proposed product has the same efficacy and safety as those of foreign-marketed products as reported in publications, etc. Therefore, in the review of the proposed product, the data from publications submitted as reference data was positioned merely as reference information.

At the Expert Discussion, the PMDA's above judgment was supported by the expert advisors.

2) Efficacy

In the Japanese open-label, uncontrolled clinical study, data of which has been submitted as the evaluation data of the present application, times to events such as overall survival (OS) were not evaluated; instead, the "level of response" evaluated using changes in serum M protein level as the index, was set as the primary endpoint.

The PMDA has concluded as follows:
Since clinical evaluation using serum M protein is widely accepted in Japan as well as overseas as an index reflecting tumor burden, it is possible to evaluate the efficacy of Thalidomide based on the "level of response." Examination of M protein-reducing effect in individual subjects in the Japanese clinical study showed a mostly favorable tendency up to 16 weeks after starting treatment. In addition, the observed M protein-reducing effect of the proposed product was not significantly

different from that reported in foreign publications using foreign-marketed products with formulations different from that of the proposed product. Based on a comprehensive consideration of these facts, etc., the proposed product is expected to be effective in Japanese patients with multiple myeloma (MM).

At the Expert Discussion, the following comments were raised from the expert advisors regarding the PMDA's judgment.

- The judgment that the proposed product is effective in reducing serum M protein level is acceptable, as shown by the results of the Japanese clinical study. In this study, the serum M protein-reducing effect was judged to be present when the response persisted for 4 weeks or more. However, there is a possibility that temporal factors such as evaluation time point and required response duration may affect the "response rate," as exemplified by the fact that the "response rate" was 35.3% (12 of 34) when assessed for the response persisting for 4 weeks or more, whereas the rate decreased to 26.5% (9 of 34) for the response persisting for 6 weeks or more. Therefore, caution should be exercised in comparing the M protein-reducing effect of the proposed product with external controls. Also, since the evaluation time point, evaluation criteria, and dosage regimen differ among publications presented in the Review Report (1), due care should be taken in comparing the effect with that of external controls. The 3 subjects who had received study treatment for less than 4 weeks and were excluded from the efficacy analysis population in the Japanese clinical study should be included in the denominator as non-responders (32.4%, 12 of 37 subjects).

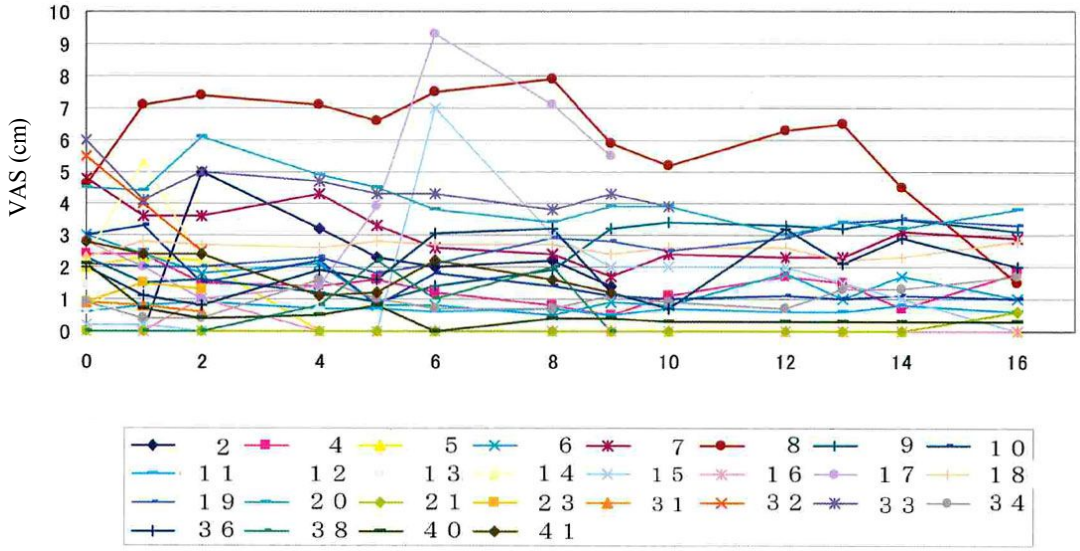
- On the basis of the collective judgment of the fact that Thalidomide is regarded as one of the options for treating MM in various guidelines and in textbooks, etc., and that there is no data showing the M protein-reducing effect of the proposed product to be markedly inferior to that of foreign-marketed products reported in publications, the proposed product is expected to be effective in patients with MM.

As a result of deliberation at the Expert Discussion, the PMDA's judgment that the proposed product was expected to be effective in Japanese patients with MM was supported by the expert advisors. Regarding the clinical usefulness of the proposed product, an opinion was expressed that since times to events such as OS were not evaluated in the Japanese clinical study, it would be necessary to collect information on OS, etc., in the post-marketing surveillance, etc., thereby allowing evaluation of the efficacy of the proposed product [see the Review Report (2) "6) Matters to be investigated after marketing"].

In addition, a comment was raised from an expert advisor that evaluation of bone pain should be performed over time in individual patients.

The PMDA checked for the change over time in bone pain VAS in 28 subjects, excluding 9 without bone pain throughout the total evaluation period, among 37 subjects included in the safety analysis, in the data from the Japanese clinical study submitted by the applicant. As a result, it was confirmed that the bone pain relieving effect of the proposed product was unclear in this study (see figure below).

Changes over time in bone pain (VAS) by subject (28 subjects)



Evaluation time point (week)

3) Safety

The PMDA considers as follows:

As a result of examination of safety information on the proposed product obtained from the Japanese clinical study, the adverse events reported in the study were manageable under supervision of physicians with knowledge and experience in the treatment of hematopoietic malignancies. However, the safety information included in the initially submitted evaluation data from the Japanese clinical study was only up to 16-week treatment, and long-term safety information over 16 weeks was then available during the regulatory review period only for 20 subjects (maximum treatment duration, 116 weeks) who proceeded to the extension study, therefore, it is necessary to accumulate information during a certain post-marketing period, by setting the entire treatment period as the surveillance period [see the Review Report (2) "6) Matters to be investigated after marketing"]. Also, since Thalidomide reportedly increases the risk of venous thromboembolism (VTE) not only in patients with a history of VTE but also in those co-administered dexamethasone or oral contraceptives, it will be necessary to advise appropriate caution in the package insert regarding co-administration with drugs for which episodes of VTE are reported as adverse drug reactions. In addition, since there is currently no information on the incidence of Thalidomide-induced VTE, nor are any appropriate preventive measures available against VTE in the Japanese, it will be necessary to collect information along this line and to take appropriate measures.

At the Expert Discussion, the above judgment of the PMDA was supported by the expert advisors. The following comments were raised from some of the expert advisors.

- Despite the expected long-term use, the safety information on the proposed product is extremely limited. Therefore, it is necessary to collect information on safety for long-term use after marketing. It is required to periodically analyze safety information and to provide such information to medical professionals in a prompt and appropriate manner, such as through the applicant's website.

- Although VTE was not a major problem in the Japanese clinical study, it is necessary to advise appropriate caution regarding VTE in the package insert since the proposed product will be used after marketing in a number of patients with various backgrounds, and probably in combination with dexamethasone and oral contraceptives. Since age, increased D dimer

level, presence of complications (diabetes, infections, cardiac disease), and poor performance status (wheel-chair bound, bedridden) are also reported to be risk factors for VTE (*Leukemia.* 2008;22:414-443), it is desirable to advise caution by providing such information to medical professionals. In the post-marketing surveillance, it is necessary to collect VTE-related information such as preventive agents used against VTE [see the Review Report (2) "6) Matters to be investigated after marketing"].

- Although hypothyroidism and gastrointestinal perforation are rare complications, patients should be closely monitored physically, taking into consideration the possible occurrence of these events.

- Since the safety information on the proposed product available from the Japanese clinical study is limited, it is necessary to advise caution to medical professionals by providing safety information from reports of foreign-marketed products in an appropriate manner, through information materials, the applicant's website, or other channels.

The PMDA instructed the applicant to address the above comments from the expert advisors, to which the applicant responded that they would appropriately address these suggestions.

4) Clinical positioning and indications

The PMDA considers as follows:

Foreign-marketed products are reported to provide better clinical study results in untreated MM patients when administered in combination with dexamethasone, etc., compared with conventional standard therapies. However, since there is currently no study data available that directly compare pharmacokinetics between the proposed product and the foreign-marketed products, it is appropriate to consider that there is currently no evidence to support the efficacy of the proposed product in untreated MM patients or in combination therapy. Therefore, on the basis of the results of the Japanese clinical study, the proposed product should be clinically positioned as one of the salvage therapies for patients in whom other therapies are ineffective or not feasible among those with MM relapsing after hematopoietic stem cell transplantation or with chemotherapy-resistant MM.

The PMDA has concluded as follows:

On the basis of the clinical positioning, the indications for the proposed product should be "relapsed or refractory multiple myeloma." It is appropriate to advise caution by describing in the "Precautions for indications" that the product should be used in patients who are non-responsive to at least 1 standard therapy or in those with relapse after treatment, and to start administration after careful consideration of other treatment options.

At the Expert Discussion, the above opinion of the PMDA regarding the indications was supported by the expert advisors.

It was pointed out by the expert advisors that the meaning of the phrase "patients who are non-responsive to at least 1 standard therapy or those with relapse after treatment" should be clarified.

The PMDA explained that the patients are assumed to be non-responders or to have relapsed MM after a standard therapy such as melphalan/prednisolone (MP therapy) or vincristine/doxorubicin/dexamethasone (VAD therapy) or after hematopoietic stem cell transplantation, and that although information available from the Japanese clinical study on the proposed product is very limited, the proposed product may be positioned as one of the salvage therapies at the current time.

The above opinion of the PMDA was supported by the expert advisors.

The following comment was also raised from the expert advisors:
A foreign long-term study found that, when 3-drug combination therapy, i.e. Thalidomide in combination with MP therapy, was administered to 65-year or older patients who are not candidates for hematopoietic stem cell transplantation, results of the initial treatment were better than those of MP therapy alone in terms of both response rate and PFS, whereas after relapse, the MP therapy group showed a response superior to that of the Thalidomide/MP therapy group to a Thalidomide- or bortezomib-based regimen, with no significant difference in final OS among these therapies (*Blood*. 2008;doi:10.1182/blood-2008-04-149427). Therefore, a consensus has not been reached regarding the optimal timing of Thalidomide use.

The PMDA's judgment that, given the lack of information on initial treatment with the proposed product, use of the product in untreated MM patients is an issue to be investigated after marketing was supported by the expert advisors.

Also, the PMDA's judgment to approve the proposed product for the indication of plasma cell neoplasm as well, which was not investigated in the Japanese clinical study, such as smoldering myeloma and non-secretory myeloma, under the condition that the information on safety and efficacy of the product in patients with these diseases be collected after marketing was supported by the expert advisors.

On the basis of the deliberation at the Expert Discussion, the PMDA instructed the applicant to set the indications and the precautions for indications as follows:

Indications: Relapsed or refractory multiple myeloma

Precautions for indications: Treatment with the product should be given to patients who are non-responsive to at least one of the standard therapies or who relapse after treatment. Treatment with the product should be started after careful consideration of other treatment options.

5) Dosage and administration
The PMDA judged it unavoidable to set the dosage and administration at 100 to 400 mg once daily, which is the dosage regimen investigated in the Japanese clinical study, for the following reasons:

a. In the Japanese clinical study, the proposed product was administered by dose titration starting from 100 mg.
b. The relationship between efficacy and dose of Thalidomide is unclear in both the Japanese clinical study and various publications.
c. The safety of the product has not been investigated at high doses, i.e. those exceeding the maximum dose (400 mg/day), which were planned in the Japanese clinical study.

Regarding foreign-marketed products with formulations different from that of the proposed product, the efficacies of Thalidomide in combination with other anti-neoplastic agents including dexamethasone have been reported in foreign publications. It is therefore expected that, after marketing, the proposed product will be used in combination with other anti-neoplastic agents in Japan as well. Since no information is currently available on combination therapy with the proposed product and other anti-neoplastic agents (including dexamethasone), it will be necessary to advise caution in this regard in the package insert.

At the Expert Discussion, the above judgment of the PMDA was supported by the expert advisors. The following comments were made by the expert advisors.

- The dose of 100 mg/day, which was used as the starting dose in the Japanese clinical study, should be clearly set as the starting dose.

- After marketing, it is likely that the proposed product is administered in combination with dexamethasone and/or other anti-neoplastic agents, by referring to the data from foreign clinical studies that used Thalidomide products with formulations different from that of the proposed product. Such combination therapy should not be prohibited; instead, it is necessary to appropriately provide medical professionals with the information that combination therapy results are not yet available for the proposed product.

- It is necessary to organize information on safety issues that have been observed with Thalidomide products other than the proposed product (including safety information on combination with dexamethasone, such as increased VTE risk), and to provide medical professionals with such information in an appropriate manner, such as through information materials or the applicant's website.

- The dose of 50 mg of the proposed product may be administered as a daily dose depending on the conditions of patients. In such situations, a drug product containing less than the 100 mg dose, the lowest limit investigated in the Japanese clinical study, may be needed in clinical practice (e.g. 50 mg formulation). Therefore, it is desirable to develop a formulation of different strength at an early date.

- The "Warnings" section in the package insert should contain a strict caution that the product should only be administered to patients in whom it is indicated, under the supervision of a physician with knowledge and experience in the treatment of hematopoietic malignancies, at a medical institution where adequate facilities for the treatment of emergencies are available. Teratogenicity, VTE risk, absolute necessity of contraceptive measures, etc., should also be included in the "Warnings."

On the basis of the above deliberation at the Expert Discussion, the PMDA instructed the applicant to set the following dosage and administration, and to revise the proposed package insert.

Dosage and administration: The usual adult dosage for oral use is 100 mg of Thalidomide once daily before bedtime. The dosage may be increased or decreased, according to the patient's condition, up to a maximum of 400 mg per day.

The PMDA also instructed the applicant to advise caution, in the "Precautions for Dosage and Administration," to assure that the treatment is started at the initial dose of 100 mg once daily, followed by titration up by 100 mg each at intervals of at least 4 weeks by taking the patient's condition into consideration, and to assure that the dose is adjusted in accordance with the criteria used in the Japanese clinical study. In addition, the PMDA instructed the applicant to advise caution, in the "Important Precautions," to assure that the risks and benefits of continued treatment are carefully weighed if the product is intended to be used over 16 weeks, because only limited information is available on administration of the proposed product over 16 weeks from the Japanese clinical study.

The applicant responded that the guideline for proper use of the proposed product would be established upon discussion with relevant academic societies and experts.

The PMDA accepted the applicant's response.

6) Matters to be investigated after marketing

The PMDA considered it appropriate that all patients who are treated with the proposed product in

the surveillance should be investigated for the entire treatment period (including the period of collecting safety information during long-term treatment), for the following reasons.

a. Adverse events associated with Thalidomide which impair QOL, such as neurotoxicity, are observed more than 16 weeks after starting treatment as well, raising concern about increased incidences with longer-term treatment.
b. Long-term safety information on the proposed product is very limited.

The PMDA considered the followings to be major information that should be collected.

- Times from the start of treatment to events such as aggravation of the primary disease, discontinuation due to an adverse event, and death

- Safety information obtained from long-term treatment over 16 weeks, including changes over time in neurological symptoms and their outcome

- Occurrence of VTE and presence or absence of anticoagulant therapy, etc., used for the prevention of VTE

- Status of combination therapy with other anti-neoplastic agents including dexamethasone, and safety information obtained from such combination therapies.

In addition, the PMDA considers as follows:
The data from the post-marketing surveillance should be analyzed at approximately 1 year after marketing to obtain necessary information, and revision of the surveillance protocol should take place based on the results of this analysis. Also, the information should be promptly provided to medical professionals through the applicant's website, etc.

At the Expert Discussion, the PMDA's opinion that the post-marketing surveillance should be conducted for the entire treatment period to include all patients treated with the proposed product was supported by the expert advisors.

An opinion was expressed by an expert advisor that there were problems in the applicant's data analysis planning as judged from the submitted data and that the advice of medical experts and biostatisticians should be sought in conducting post-marketing surveillance and clinical studies, and in analyzing the results.

On the basis of the results of the above deliberation, the PMDA instructed the applicant that for a certain period of time after marketing, the post-marketing surveillance be conducted for all patients treated with the proposed product for their entire treatment period. In addition, the PMDA instructed the applicant to seek the advice of medical experts and biostatisticians from the planning stage of the post-marketing surveillance and clinical studies and to perform data analysis in an appropriate manner.

7) Post-marketing clinical study
As a post-marketing clinical study, the applicant plans to conduct a multi-center, randomized, open-label study with a central registration system, in patients with relapsed or refractory MM (target number of patients, 180; 90 per group), setting time to progression (TTP), progression-free survival (PFS), and OS as primary endpoints, using high-dose dexamethasone, which is already widely used for the treatment of MM in clinical practice in Japan and overseas, as a control.

The PMDA presented the following consideration:
The protocol presented by the applicant has problems such as setting up 3 different primary

endpoints. There were also protocol violations in some subjects in the clinical study that the applicant conducted for the present application. In light of these facts, there is a concern about the feasibility of the post-marketing clinical study planned by the applicant. However, it is necessary to collect time-to-event information after marketing because no information was obtained regarding OS improvement with the proposed product from the Japanese clinical study data submitted at approval application. Thus, since there are many issues that should be investigated, including the effect of the proposed product on the OS of patients with relapsed or refractory MM, it is necessary to analyze, in advance, the information to be obtained from the post-marketing surveillance, and then to consider the protocol for the post-marketing clinical study.

At the Expert Discussion, the following opinions were expressed by the expert advisors regarding the above judgment of the PMDA.

- There are doubts about the feasibility and scientific justification of the clinical study, as judged by the protocol outline presented by the applicant, for example, the setting of target patients, control group, primary endpoints, etc. These facts indicate that the study plan presented for review is inappropriate and not sufficiently concrete, raising grave concern about the stance of the applicant as a company involved in the development of pharmaceutical products.

- It will be feasible to use PFS, TTP, etc., as the primary endpoints in untreated MM patients in the post-marketing clinical study. However, setting-up of an appropriate control group should be considered based on the collective opinions of related academic societies and experts.

- The 8-year survival rate reportedly improved significantly with Thalidomide treatment both before and after high-dose chemotherapy and this improving effect was also observed in patients with cytogenetic abnormalities (*N Engl J Med.* 2008;359:210-212). It is desirable to evaluate the usefulness of the proposed product in Japanese patients for whom high-dose chemotherapy is indicated.

On the basis of the deliberation at the Expert Discussion, the PMDA instructed the applicant to analyze the information to be obtained from a certain period of post-marketing surveillance, and in parallel to work out an appropriate clinical study plan based on the opinions of related academic societies, medical experts, and biostatisticians.

8) Pharmacokinetics

The PMDA judged as follows:

Effects of food on PK will be a matter of concern in administering the drug in clinical practice. Since these effects can be estimated at present only from the results of biopharmaceutical studies using foreign-marketed products with formulations different from that of the proposed product, the exact effect of the proposed product on PK is unknown. Also, information on the PK of the proposed product is available only regarding administration of 100 mg in a single dose. It is difficult to accurately ascertain, from the findings obtained with foreign-marketed products, the PK of the proposed product, for clinical doses other than 100 mg (for which no information has been obtained) and that of multiple doses (to assess accumulation of the product). Therefore, it is necessary to promptly investigate the PK of the proposed product when ingested together with food, the PK of doses other than 100 mg, and the PK after multiple doses, and to provide medical professionals with the results of the clinical study in an appropriate manner.

At the Expert Discussion, the above judgment of the PMDA was supported by the expert advisors. Also, the following opinions were expressed by the expert advisors.

- PK of a drug within its clinical dose range (100-400 mg/day for the proposed product) and PK after multiple doses are basic information in drug development. In addition, effects of food on PK are essential even in the clinical development of drugs intended to be used before bedtime. Therefore, these matters should be investigated.

- PK studies are feasible, if the cooperation of patients is obtained; it is not appropriate to study PK in healthy adults.

On the basis of the above opinions, the PMDA instructed the applicant to conduct PK studies.

The following comment was also made by the expert advisors:
Regarding the non-clinical pharmacokinetic study, the applicant considers Thalidomide to be well absorbed, judging from the results of the *in vitro* study using Caco-2 cells that showed dose-dependent permeability of the drug [see the Review Report (1) "3.2 Pharmacokinetic data"]. However, the apparent permeability coefficient decreased dose-dependently within a certain dose range according to one of the publications cited by the applicant, which suggests that the explanation of the applicant is not appropriate.

Although all data related to non-clinical pharmacokinetics are reference data, the PMDA considers the discussion of the applicant to be inappropriate in that no consideration was given to the difference in study conditions, etc. [see the Review Report (1) "3.2 Pharmacokinetic data"].

9) Others
At the Expert Discussion, the following comments were raised from the expert advisors.

- The PMDA's judgment that the risk of not approving the proposed product outweighs the risk of approving the product from the viewpoint of public health is appropriate. However, it is essential that information on the safety and efficacy of the product be accumulated by post-marketing all-case surveillance and other means, on the premise that a post-marketing safety management system for the product, which is being examined separately at the Ministry of Health, Labour and Welfare, will be implemented in an appropriate manner.

- In the report on the Japanese clinical study, it is stated that, "there were 6 subjects in whom specific contraceptive method could not be identified" [see the Review Report (1) 4.3.B.8) Contraception"]. It is a matter of concern that an investigator in the study stated to the monitor of the applicant that "you have no right to ask such a question," showing the lack of awareness of participants in the study. In order to use the proposed product appropriately, it is important to realize that not only patients and their families but also the regulatory agency, the company, and medical professionals are concerned parties. For this purpose as well, it is essential that the post-marketing safety management system for the product, which is being examined separately at the Ministry of Health, Labour and Welfare, be implemented in an appropriate manner.

On the basis of the above comments from expert advisors, the PMDA considers the contraceptive measures, as follows:
Whereas avoiding teratogenicity should be recognized as the most important issue in the proper use of Thalidomide, the applicant's effort was insufficient in the collection and analysis of information on this issue in the Japanese clinical study. VTE is recognized as an adverse reaction to oral contraceptives, which raises concern about the increased risk of VTE when oral contraceptives are co-administered with the proposed product. Thus, it is important after marketing to select a contraceptive method by taking into consideration the characteristics of each method and patient so that contraception is practiced effectively and safely. Not only medical professionals but also the applicant should bear great responsibility to ensure the education of patients and their

partners.

10) Errors in the description in the application dossier

The proposed product is an item that was deliberated upon at the meeting of the Investigational Committee for Usage of Unapproved Drugs. A petition for prompt approval had been filed by concerned parties including a patient group to the Minister of Health, Labour and Welfare. However, the data attached to the approval application contained quite a few subjects with protocol violations. In addition, the in-house check system of the applicant was not stipulated in the standard operating procedures, etc., resulting in more than 100 errors in the data submitted at application. Furthermore, problems arose during the review, such as repeatedly providing ambiguous responses to some of the questions from the PMDA, resulting in repeated revisions of the application dossier and of responses to questions after submission. It may be said without exaggeration that the fact that so many changes had to be made in the application dossier proves that no thorough quality control or assurance had been performed in filing the application or responding to the questions. In the present review, a huge amount of time and work had to be invested in repeated checks of these revisions, interfering with the conduct of an efficient review. In the future, the applicant should more fully recognize the importance of quality control and assurance of the application dossier and promptly organize the appropriate system for quality control and assurance.

III. Overall Evaluation

Since teratogenicity (Thalidomide embryopathy) has been reported with clinical use of Thalidomide, it is critical in using the proposed product in clinical practice to comply with the safety management system currently being examined separately.

The PMDA has concluded that the proposed product may be approved for the following indications and dosage and administration, on the premise that the safety management system for Thalidomide being examined separately is complied with, that cautions are advised in the package insert, that information regarding proper use are provided in an appropriate manner after marketing, and that the product is appropriately used under the supervision of a physician with knowledge and experience at a medical institution where adequate facilities for the treatment of emergencies are available, with the following conditions for approval.

Since the product of the present application is a drug with a new active ingredient designated as an orphan drug, it is appropriate to set the re-examination period as 10 years and to designate both the drug substance and the drug product as poisonous drugs. The product is not to be classified as a biological product or a specified biological product.

[Indications]

Relapsed or refractory multiple myeloma

[Dosage and administration]

The usual adult dosage for oral use is 100 mg of Thalidomide once daily before bedtime. The dosage may be increased or decreased, according to the patient's condition, up to a maximum of 400 mg per day.

[Conditions for approval]

1. Strict and appropriate measures should be taken to assure that the product is administered only to patients in whom the treatment is judged adequate, under the supervision of a physician with knowledge and experience at a medical institution where adequate facilities for the treatment of emergencies are available, after each patient and/or his/her family members have been provided with written information on the efficacy and risks of the treatment and have given written informed consent in advance.

2. Because of the very limited number of patients investigated in the Japanese clinical study, a drug use investigation should be carried out on all patients treated with the product after marketing until data has been accumulated from a certain number of patients, and the results should be published periodically. After a certain period of time has passed since the marketing, data related to the safety and efficacy of the product should be collected expeditiously, such as by conducting appropriate clinical studies, based on the information obtained at each time point and on the comments of medical experts and biostatisticians, and appropriate measures should be taken to assure proper use of the product.

[Instruction]
An appropriately designed study should be conducted to further clarify the pharmacokinetics of the proposed product and the results should be published.

[Warnings]
1. The product is known to be teratogenic in humans (Thalidomide embryopathy), and administration during pregnancy may cause serious fetal malformations, abortion, or stillbirth. Therefore, the product should never be administered to pregnant or possibly pregnant women (see "CONTRAINDICATIONS" and "Use during Pregnancy, Delivery or Lactation").

2. Safety management criteria have been established for use of the product to minimize fetal exposure to the product. All concerned parties including related companies, medical professionals such as physicians and pharmacists, patients, and their family members must comply with these criteria (see "CONTRAINDICATIONS").

3. In administering the product to women with child-bearing potential, a pregnancy test must be performed in advance, and administration should be started only when a negative test result has been confirmed. It must be assured that both the patient and his/her partner, if engaged in sexual activity, take maximally effective contraceptive measures (men must use latex condoms) during the period between 4 weeks before start of administration and 8 weeks after completion of administration, and physicians should thoroughly confirm their compliance and periodically conduct pregnancy tests (see "Important Precautions (1)").
   The patient must be instructed to immediately discontinue taking the product in the event that pregnancy is suspected, and to consult a physician, etc.

4. The product is secreted into seminal fluid. Therefore, when administering the product to male patients, they and their partners must be instructed to, if engaged in sexual activity, take maximally effective contraceptive measures (men must use latex condoms), and physicians must thoroughly confirm their compliance.

5. The product should be administered only to patients in whom the treatment is judged adequate, under the supervision of a physician with knowledge and experience at a medical institution where adequate facilities for the treatment of emergencies are available. Prior to treatment, patients and/or their family members must be provided with detailed explanations of the efficacy and risks (including the risks of fetal exposure to the product), and must give written informed consent.

6. The product may cause deep vein thrombosis. Therefore, the product must be administered with care while closely observing the patient's clinical condition. If any abnormalities are observed, administration of the product should immediately be discontinued, and appropriate measures taken.

[Precautions for indications]
The product should be used in patients with multiple myeloma who are non-responsive to at least 1 standard therapy or those with relapse after treatment. Administration of the product should be started after careful consideration of other treatment options.

[Precautions for dosage and administration]
(1) Administration of the product should be started at 100 mg once daily. When efficacy is insufficient, the dose should be titrated up by 100 mg each at 4-week intervals.
(2) There are only limited data available regarding the efficacy and safety of the product administered over 16 weeks. If the product is intended to be used over 16 weeks, careful consideration should be given to the risks and benefits of continued treatment.
(3) When the dose of the product is adjusted, consideration should be given to the following criteria for dose reduction, dose interruption, and discontinuation employed in the Japanese clinical study.

Dose	Dose interruption/dose reduction	Discontinuation
100 mg	Dose interruption: When Grade 2 non-hematological toxicity or Grade 3 hematological toxicity is observed.	Deep vein thrombosis, Grade 4 hematological toxicity, or Grade ≥ 3 non-hematological toxicity
≥ 200 mg	Dose reduction: The dose is to be reduced by 100 mg if Grade 2 non-hematological toxicity or Grade 3 hematological toxicity is observed, and the dose is to be reduced by a further 100 mg if no recovery from or improvement of symptoms is observed 1 week after the dose reduction.	

(The definition of Grade conforms to that of the Common Terminology Criteria for Adverse Events, v3.0, Japanese translation (JCOG/JSCO). Hematological toxicity and non-hematological toxicity refer to adverse events for which a causal relationship to the product cannot be denied.)