Patent Right	Date	July 2, 2020	Court	Intellectual Property High Court, Third Division
	Case number	2018(Gyo-Ke) 10158, 10113		
- A case in which it was determined that a determination of a trial decision that an invention does not comply with the support requirement was erroneous. - A case in which it was determined that a determination of a trial decision that an invention does not lack an inventive step was not erroneous.				

Case type: Rescission of Trial Decision of Invalidation

Result: Granted

References: Article 36, paragraph (6), item (i) of the Patent Act, Article 29, paragraph (2) of the Patent Act

Related rights, etc.: Patent No. 4162491

Decision of JPO: Invalidation Trial No. 2016-800096

Summary of the Judgment

1. The present case is a lawsuit for rescission of a trial decision for a trial for patent invalidation concerning the invention of "FORMULATION OF BORONIC ACID COMPOUNDS". The trial decision determined that there is no ground for invalidation due to lack of an inventive step of the invention, but there is a ground for invalidation due to non-compliance with the support requirement.

2. This judgment held on the support requirement as follows, and held that it was erroneous for the trial decision to determine that the invention does not comply with the support requirement.

(1) Procedure for Determination on Compliance with the Support Requirement

A determination on whether the statement of the Scope of Claims complies with the support requirement of the description shall be made as follows. First, a comparison is made between the statement of the Scope of Claims and the statement of the Detailed Description of the Invention. Then, a consideration is made on whether or not the invention stated in the Scope of Claims is the invention stated in the Detailed Description of the Invention, and is within the scope where a person ordinarily skilled in the art can recognize that the statement or the suggestion of the Detailed Description of the Invention can solve the problem of the invention, and even if there is neither such statement nor such suggestion, whether or not the invention stated in the Scope of Claims is within the scope where a person ordinarily skilled in the art can recognize that the problem of the invention can be solved in light of common general technical knowledge at the time of filing the application. Based on the comparison and the

consideration as mentioned above, the determination on the compliance with the support requirement shall be made.

In order to comply with the support requirement, it is construed that it is sufficient for a person ordinarily skilled in the art, who has read the description, to reasonably recognize that the claimed invention is stated in the description. With regard to the solution to the problem, it is construed that it is sufficient to state the solution to the problem to the extent that a person ordinarily skilled in the art can reasonably expect that the problem can be solved in light of common general technical knowledge, and it is construed that it is not necessary to state the extent to which the statement reaches a rigorous scientific proof. This is because the support requirement is derived from the essence of the patent system, which grants a patent right as a reward for laying the invention open to the public, and therefore the purpose of imposing the support requirement can be achieved to some extent if a person ordinarily skilled in the art, who has read the description, can contribute to the further development of the art by conducting a retest and an analysis of the invention. In addition, this is also because it is not reasonable to require that the contents of the description be demonstrated to the same degree of rigor as required in a scientific paper, taking into consideration that the description is prepared under the time constraints of the first-to-file system.

(2) Problem of the Present Invention

According to the statement of the present description, the problem to be solved by the present invention is to provide the present compound (bortezomib mannitol ester in the form of a lyophilized powder) which can be a stable pharmaceutical agent when formulated and which can be a composition which readily releases a boronic acid compound upon dissolution in aqueous media. In order that it can be deemed that this problem has been solved, it is construed that it is necessary that a considerable amount of bortezomib mannitol ester in the form of a lyophilized powder has been produced, and that the bortezomib mannitol ester has certain levels of storage stability, easiness of dissolution, and easiness of hydrolysis. Therefore, it will be considered whether it can be deemed that these points are stated or suggested in the present description in the sense as mentioned in the above (1). It should be noted that the "considerable amount" as used herein means an amount which can provide a solution to the above problem as a pharmaceutical agent.

(3) Determination Results on Compliance with the Support Requirement

It can be deemed that in light of common general technical knowledge at the time of filing the present application, a person ordinarily skilled in the art can understand from the statement, etc. in the working examples in the present description that the

present invention can solve the above problem in the sense as mentioned in the above (1).

3. With regard to an inventive step, this judgment upheld the determination of the trial decision that it cannot be deemed that the invention lacks an inventive step.

Judgment rendered on July 2, 2020
2018 (Gyo-Ke) 10158 A case of seeking rescission of the JPO decision (Case A)
2018 (Gyo-Ke) 10113 A case of seeking rescission of the JPO decision (Case B)
Date of Conclusion of Oral Argument: March 3, 2020

Judgment

Plaintiff of Case A, Defendant of Case B: The United States of America

Defendant of Case A, Plaintiff of Case B: TAKATA Pharmaceutical Co., Ltd.

Main text

1. In the trial decision rendered by the Japan Patent Office on June 25, 2018 in the case of Invalidation Trial No. 2016-800096, a portion of "the patent with regard to the inventions according to Claims 17, 19, 20, 44, and 46 of Patent No. 4162491 shall be invalidated" shall be rescinded.
2. The claim by the Plaintiff of Case B, TAKATA Pharmaceutical Co., Ltd., shall be dismissed.
3. The court costs shall be borne by the Defendant of Case A and the Plaintiff of Case B, TAKATA Pharmaceutical Co., Ltd., through Cases A and B.

Facts and reasons

No. 1 Claim

(Case A)

The same effect as the main text, the first paragraph.

(Case B)

In the trial decision rendered by the Japan Patent Office on June 25, 2018 in the case of Invalidation Trial No. 2016-800096, a portion of "the request for the trial with regard to the inventions according to Claims 21 and 38 to 42 of Patent No. 4162491 is groundless" shall be rescinded.

No. 2 Outline of the case

1. History of procedures in the Japan Patent Office

(1) The United States of America (hereinafter referred to as the "Patentee"), who is the Plaintiff of Case A and the Defendant of Case B, filed a patent application with regard to an invention titled "FORMULATION OF BORONIC ACID COMPOUNDS" on an international filing date of January 25, 2002 (received by the foreign patent office for claiming priority under the Paris Convention: the United States of America (US) on January 25, 2001). On August 1, 2008, the Patentee obtained a registration establishing a patent right as Patent No. 4162491 (hereinafter referred to as the "Patent").

(2) TAKATA Pharmaceutical Co., Ltd. (hereinafter referred to as "Demandant TAKATA"), who is the Defendant of Case A and the Plaintiff of Case B, demanded a trial for invalidation (Invalidation Trial No. 2016-800096) with regard to the Patent on August 5, 2016.

In the proceedings for the trial for invalidation, the Patentee filed a request for correction for the purpose of restricting the scope of claims, etc.

The Japan Patent Office rendered a trial decision on June 25, 2018. A period of 90 days was added as a time limit of action against the trial decision for the Patentee.

(3) The conclusion of the trial decision was as follows.

"The correction of the scope of claims of Patent No. 4162491 shall be approved with regard to corrected Claims [1 to 20], [21 to 43, 45, 47], 44, and 46 as stated in the corrected scope of claims attached to the written correction request.

The patent with regard to the inventions according to Claims 17, 19, 20, 44, and 46 of Patent No. 4162491 shall be invalidated.

The request for the trial with regard to the inventions according to Claims 21 and 38 to 42 of Patent No. 4162491 is groundless.

The request for the trial with regard to the inventions according to Claims 1 to 16, 18, 22 to 37, 43, 45, and 47 of Patent No. 4162491 shall be dismissed."

(4) On July 5, 2018, the trial decision was served on the Patentee. In response to this, on November 2, 2018, the Patentee filed a lawsuit for seeking a rescission of a portion of the trial decision in which the patent shall be invalidated (Case A).

On July 4, 2018, the trial decision was served on the Demandant TAKATA. In response to this, on August 3, 2018, the Demandant TAKATA filed a lawsuit for seeking a rescission of a portion of the trial decision in which the request for the trial was groundless (Case B).

2. Statement of the scope of claims

(1) The determination of the trial decision on the request for correction (approving the request for correction and dismissing the request for the trial for invalidation with regard to the claims deleted by the correction) is not in dispute by the two parties.

(2) Corrected Claims 17, 19, 20, 44, and 46 are inventions of a product. In connection with the assertion of reasons for rescission of the trial decision in the present case, if the determination of the trial decision on corrected Claim 17 is erroneous, the determination on other claims will also be erroneous.

The statement of corrected Claim 17 is as follows (hereinafter referred to as the "Invention of the Present Compound").

[Claim 17]

D-mannitol N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate in the form of a lyophilized powder.

(3) Corrected Claims 21 and 38 to 42 are inventions of a process. In connection with the assertion of reasons for rescission of the trial decision in the present case, if the determination of the trial decision on corrected Claim 21 is erroneous, the determination on other claims will also be erroneous.

The statement of corrected Claim 21 is as follows (hereinafter referred to as the "Invention of the Present Production Method").

[Claim 21]

A method of preparing D-mannitol N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate in the form of a lyophilized powder, the method comprising:

(a) preparing a mixture comprising

(i) water,

(ii) N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid, and

(iii) D-mannitol; and

(b) lyophilizing the mixture.

(4) Hereinafter, "N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid" will be referred to as "bortezomib" or "Bz".

Further, "D-mannitol N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate" is an ester compound of bortezomib and D-mannitol, and hereinafter will be referred to as "bortezomib mannitol ester" or "BME".

The Invention of the Present Compound and the Invention of the Present Production Method (hereinafter also referred to collectively as "the Present Invention") are represented by the following abbreviations, respectively.

[Invention of the Present Compound]

BME in the form of a lyophilized powder

[Invention of the Present Production Method]

A method of preparing BME in the form of a lyophilized powder, the method comprising:

(a) preparing a mixture comprising

(i) water,

(ii) bortezomib, and

(iii) D-mannitol; and

(b) lyophilizing the mixture.

3. Summary of reasons of the trial decision

The summary of reasons of the trial decision (only the portion related to the reasons for rescission of the trial decision as asserted in this lawsuit) is as follows.

(1) Reason 1 for Invalidation (Lack of inventive step (No. 1))

[Demandant TAKATA's assertion]

The Present Invention could have been easily made by a person ordinarily skilled in the art on the basis of the publicly known invention as disclosed in Exhibit Ko 7 (Sara Wu, et al., JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 89, NO. 6, JUNE 2000) and the well-known art.

[Determination of the trial decision]

(The summary of the determination on the Invention of the Present Compound is given below, and the same effect substantially applies to the Invention of the Present Production Method.)

A. Findings on the cited invention

Exhibit Ko 7 discloses an invention of a "peptide boronic acid derivative 2-Pyz-(CO)-Phe-Leu-$B(OH)_2$" (hereinafter referred to as "Exhibit Ko 7 Invention").

B. Comparison

[Common Feature]

A peptide boronic acid derivative compound.

[Different Feature 1]

In the Invention of the Present Compound, the peptide boronic acid derivative compound is BME, which is an ester of bortezomib with D-mannitol. On the other hand, in the Exhibit Ko 7 Invention, the peptide boronic acid derivative compound is bortezomib.

[Different Feature 2]

In the Invention of the Present Compound, the compound is specified as being

in "the form of a lyophilized powder". On the other hand, in the Exhibit Ko 7 Invention, the compound is not specified as such.

C. Whether Different Features would have been easily conceivable

With regard to Different Feature 1, Exhibit Ko 7 is a document concerning the degradation pathway of bortezomib, and does not disclose anything about synthesizing and producing another compound from bortezomib as a raw material.

With regard to Different Feature 2, Exhibit Ko 7 does not specifically disclose lyophilizing bortezomib to obtain a lyophilized powder. In addition, a means of improving stability and water solubility when formulating a product is not limited to lyophilization. Further, there are various options for fillers to be used in lyophilization. Thus, as a means of improving stability and water solubility, it cannot be deemed that it is a matter of well-known art that lyophilization is performed by using mannitol as an additive.

Furthermore, even if lyophilizing bortezomib with mannitol would have been conceived of, it would not have been easily conceivable to perform lyophilization to obtain BME instead of bortezomib, in view of the common general technical knowledge that lyophilization is performed with the intention of not changing a structure of a target compound.

D. As mentioned above, in view of the common general technical knowledge and the well-known art in addition to the disclosure of Exhibit Ko 7, it cannot be deemed that it would have been easily conceivable to react bortezomib with D-mannitol to obtain BME in the form of a lyophilized powder.

Therefore, with regard to the Invention of the Present Compound, the Demandant TAKATA's assertion concerning Reason 1 for Invalidation is groundless.

(2) Reason 2 for Invalidation (Violation of support requirement (No. 1))

[Demandant TAKATA's assertion]

The problem to be solved by the Present Invention is "to provide an improved formulation of a boronic acid compound having stability and reconstitution property."

However, the detailed description of the invention only states that an ester of a boronic acid and a sugar was formed under the specific lyophilization conditions of the Examples, and that the above-mentioned problem was solved. It cannot be inferred that a lyophilized formulation obtained under lyophilization conditions other than those of the Examples can solve the above-mentioned problem. This lyophilized formulation can be neither expanded nor generalized to the scope of the invention stated in the claims of the Patent.

Therefore, the statement of the scope of claims of the Patent violates the

support requirement.

[Determination of the trial decision]

With regard to the Invention of the Present Compound, the problem to be solved by the Present Invention is "to provide BME in the form of a lyophilized powder, which can be a stable pharmaceutical agent when formulated and which can be a composition (with excellent reconstitution property) which readily releases a boronic acid compound upon dissolution in an aqueous medium." In addition, with regard to the Invention of the Present Production Method, the problem to be solved by the Present Invention is "to provide a method of preparing BME in the form of a lyophilized powder." Therefore, the Demandant TAKATA's assertion on the problem cannot be accepted.

Furthermore, the Demandant TAKATA refers to Exhibit Ko 19 (experimental report (prepared by Sandoz AG on January 26, 2015)) as the grounds that BME obtained by lyophilization does not have reconstitution property. However, it has not been confirmed that the sample which was found to have inferior reconstitution property in this experiment contains "BME in the form of a lyophilized powder" according to the Present Invention. Thus, from Exhibit Ko 19, it cannot be deemed that BME in the form of a lyophilized powder does not have reconstitution property.

Therefore, the Demandant TAKATA's assertion cannot be accepted.

(3) Reason 4 for Invalidation (Lack of inventive step (No. 2))

(This is a reason for invalidation of the Invention of the Present Compound, but it is not a reason for invalidation of the Invention of the Present Production Method.)

[Demandant TAKATA's assertion]

The Invention of the Present Compound is a selection invention of the publicly known invention as disclosed in Exhibit Ko 1 (National Publication of International Patent Application No. 1998-510245). In order for a selection invention to be acknowledged as having an inventive step, it is necessary for the invention to have a qualitatively different effect from the cited invention, or to have an effect that is qualitatively the same but remarkably excellent. However, an effect of the Invention of the Present Compound is unclear. Therefore, an inventive step cannot be acknowledged.

[Determination of the trial decision]

A. Findings on the cited invention

Exhibit Ko 1 discloses an invention of a boronate ester of bortezomib (hereinafter referred to as the "Exhibit Ko 1 Invention").

B. Comparison

[Common Feature]

A boronate ester of bortezomib.

[Different Feature 1]

In the Invention of the Present Compound, the boronate ester of bortezomib is an ester with D-mannitol. On the other hand, in the Exhibit Ko 1 Invention, the boronate ester of bortezomib is not specified as an ester with D-mannitol.

[Different Feature 2]

In the Invention of the Present Compound, the form is a lyophilized powder. On the other hand, in the Exhibit Ko 1 Invention, the form is not specified.

C. Whether the Different Features would have been easily conceivable

(a) Different Feature 1

With regard to hydroxy compounds which can be esterified with a boronic acid such as bortezomib to form a boronate ester in the Exhibit Ko 1 Invention, Exhibit Ko 1 merely specifically discloses pinanediol and the like. In the presence of numerous hydroxy compounds, Exhibit Ko 1 does not disclose the motivation to select D-mannitol which is not disclosed in Exhibit Ko 1. In addition, it cannot be found that such selection is a matter of common general technical knowledge. Thus, remarkable ingenuity is required in order to conceive of an ester with D-mannitol from the disclosure in Exhibit Ko 1.

(b) Different Feature 2

Exhibit Ko 1 discloses lyophilizing a drug. However, Exhibit Ko 1 neither discloses nor suggests an ester of bortezomib with D-mannitol. In addition, it cannot be found that lyophilizing with mannitol as an additive is a matter of well-known art as a means of improving stability and water solubility. Thus, it cannot be deemed that a person ordinarily skilled in the art could have easily obtained such an ester in the form of a lyophilized powder.

D. Demandant TAKATA's assertion on the selection invention

Since there is the above-mentioned Different Feature 2 between the Invention of the Present Compound and the Exhibit Ko 1 Invention, the Invention of the Present Compound cannot be a selection invention of the Exhibit Ko 1 Invention. Thus, the Demandant TAKATA's assertion is erroneous in its premise. Incidentally, it cannot be deemed that lyophilization technology is a matter of well-known art in the field of formulation technology. Thus, it cannot also be deemed that Different Feature 2 is not a substantial difference.

Therefore, the Demandant TAKATA's assertion cannot be accepted.

E. As mentioned above, the Demandant TAKATA's assertion concerning

Reason 4 for Invalidation is groundless.

(4) Reason 5 for Invalidation (Violation of support requirement (No. 2))

[Demandant TAKATA's assertion]

The statement in the "detailed description of the invention" of the description of the Patent (Exhibit Ko 74, hereinafter referred to as the "Present Description") does not show that BME in the form of a lyophilized powder solves the problem of the invention. Therefore, the statement of the scope of claims of the Patent violates the support requirement.

[Determination of the trial decision]

A. Invention of the Present Compound

(a) According to the statement of the Present Description, the problem of the Invention of the Present Compound is to provide "BME in the form of a lyophilized powder" which can be a stable pharmaceutical agent when formulated and which can be a composition (with excellent reconstitution property) which readily releases a boronic acid compound upon dissolution in an aqueous medium.

(b) It is a matter of common general technical knowledge that when a drug is lyophilized with an expectation of improving stability and good reconstitution property of the drug, the chemical structure of the drug itself does not change (or is not allowed to change) before and after the lyophilization. Therefore, a person ordinarily skilled in the art expects that a lyophilized product obtained by lyophilizing a drug bortezomib with mannitol will contain bortezomib whose chemical structure has not been changed, and that lyophilizing results in improved stability and good reconstitution property of bortezomib.

(c) The Patentee asserts that according to the "detailed description of the invention" in the Present Description, it is understood that a lyophilized product obtained by lyophilizing bortezomib with mannitol contains BME [0086], this lyophilized product was stable for 18 months [0096], this lyophilized product readily dissolves in water and contains bortezomib in its aqueous solution [0088], and this aqueous solution exhibits proteasome inhibition activity which is characteristic of bortezomib [0090]. Thus, the Patentee asserts that it can be deemed that the "detailed description of the invention" in the Present Description states that the problem of the invention, which is to provide a lyophilized powder as a formulation having stability and reconstitution property (the above (a)), has been solved by the Invention of the Present Compound.

However, taking into consideration the common general technical knowledge and the expectation of a person ordinarily skilled in the art as mentioned in the above

(b), the statement of [0086] only indicates that the lyophilized product contains BME, but does not exclude the possibility that the lyophilized product may additionally contain a considerable amount of bortezomib in a non-esterified state. In addition, it can be sufficiently established to be understood that the stability [0096] and the solubility [0088] exhibited by the lyophilized product are merely effects caused by lyophilizing bortezomib, to understand that the bortezomib detected in the aqueous solution [0088] was derived from bortezomib which was not esterified during the lyophilization process, or to understand that the proteasome inhibition activity exhibited by the aqueous solution [0090] is due to bortezomib which was not esterified during the lyophilization process. This is because in the statement of the Present Description, BME in the lyophilized product is not isolated and quantified [0086], and the stability and the reconstitution property are not verified for an isolated BME [0088, 0090, 0096].

Thus, the Invention of the Present Compound (BME in the form of a lyophilized powder) does not fall within the scope where a person ordinarily skilled in the art can recognize that the statement in the detailed description of the invention can solve the problem of the invention. Therefore, the Patentee's assertion as mentioned above cannot be accepted.

For the foregoing reasons, the Invention of the Present Compound does not comply with the support requirement.

B. Invention of the Present Production Method

The problem of the Invention of the Present Production Method is to provide a method of producing BME in the form of a lyophilized powder. According to the statement in [0084] and [0086] of the Present Description, it is stated in [0086] that the substance prepared by the method as stated in [0084] contains BME in the form of a lyophilized powder. Thus, the Invention of the Present Production Method is the invention stated in the detailed description of the invention, and falls within the scope where a person ordinarily skilled in the art can recognize that the statement in the detailed description of the invention can solve the problem of the invention.

Therefore, the Invention of the Present Production Method complies with the support requirement.

C. According to the above, the Demandant TAKATA's assertion concerning Reason 5 for Invalidation is well-founded with regard to the Invention of the Present Compound, but is groundless with regard to the Invention of the Present Production Method.

No. 3 Issues (Reasons for rescission of the trial decision)

1. Reasons for rescission of the trial decision asserted by the Patentee (Case A)

It is erroneous for the trial decision to determine that the patent with regard to the Invention of the Present Compound is invalid on the basis of Reason 5 for Invalidation (Violation of the support requirement (No. 2)) (hereinafter referred to as "Reasons for Rescission by the Patentee").

2. Reasons for rescission of the trial decision asserted by the Demandant TAKATA (Case B)

Among the determinations in the trial decision to maintain the patent with regard to the Invention of the Present Production Method by rejecting the reasons for invalidation, the determinations on the following reasons for invalidation are erroneous (hereinafter, in order, referred to as "Reason 1 for Rescission by the Demandant TAKATA" and the like).

(1) Reasons 2 and 5 for Invalidation (Violation of the support requirement (No. 1) and (No. 2))

(2) Reason 4 for Invalidation (Lack of inventive step (No. 2))

(3) Reason 1 for Invalidation (Lack of inventive step (No. 1))

(omitted)

No. 5 Judgment of this court

1. Reasons for Rescission by the Patentee

(1) Procedure for determination on compliance with the support requirement

A determination on whether the statement of the scope of claims complies with the support requirement of the description shall be made as follows. First, a comparison is made between the statement of the scope of claims and the statement of the detailed description of the invention. Then, a consideration is made on whether or not the invention stated in the scope of claims is the invention stated in the detailed description of the invention, and is within the scope where a person ordinarily skilled in the art can recognize that the statement or the suggestion of the detailed description of the invention can solve the problem of the invention, and even if there is neither such statement nor such suggestion, whether or not the invention stated in the scope of claims is within the scope where a person ordinarily skilled in the art can recognize that the problem of the invention can be solved in light of the common general technical knowledge at the time of filing the application. Based on the comparison

and the consideration as mentioned above, the determination on the compliance with the support requirement shall be made.

In order to comply with the support requirement, it is construed that it is sufficient for a person ordinarily skilled in the art, who has read the description, to reasonably recognize that the claimed invention is stated in the description. With regard to the solution to the problem, it is construed that it is sufficient to state the solution to the problem to the extent that a person ordinarily skilled in the art can reasonably expect that the problem can be solved in light of the common general technical knowledge, and it is construed that it is not necessary that the statement reaches the level of a rigorous scientific proof. This is because the support requirement is derived from the essence of the patent system, which grants a patent right as a reward for laying the invention open to the public, and therefore the purpose of imposing the support requirement can be achieved to some extent if a person ordinarily skilled in the art, who has read the description, can contribute to the further development of the art by conducting a retest and an analysis of the invention. In addition, this is also because it is not reasonable to require that the contents of the description be demonstrated to the same degree of rigor as required in a scientific paper, taking into consideration that the description is prepared under the time constraints of the first-to-file system.

(2) Problem of the Invention of the Present Compound

According to the statement of the Present Description, the problem to be solved by the Invention of the Present Compound is to provide the present compound (BME in the form of a lyophilized powder) which can be a stable pharmaceutical agent when formulated and which can be a composition which readily releases a boronic acid compound upon dissolution in an aqueous medium. In order that it can be deemed that this problem has been solved, it is construed that it is necessary that a considerable amount of BME in the state of a lyophilized powder has been produced, and that the BME has storage stability, easiness of dissolution, and easiness of hydrolysis. Therefore, it will be considered whether it can be deemed that these points are stated or suggested in the Present Description in the sense as explained in the above (1). It should be noted that the "considerable amount" as used herein means an amount which can provide a means for solving the above-mentioned problem as a pharmaceutical agent.

(3) Considerable amount of BME in the state of a lyophilized powder was produced

A. The Present Description discloses a method for preparing a lyophilized

formulation of bortezomib and D-mannitol as Example 1 in [0084]. In light of the common general technical knowledge as of the filing date of the present application, it can be understood that under the condition of a high ratio of tert-butanol (relatively low ratio of water) and stirring in a mixed solution containing an excess of mannitol at a temperature higher than the ambient temperature as in the above method of preparing, an esterification reaction between bortezomib and mannitol will proceed to produce a considerable amount of BME.

In addition, the Present Description discloses in [0086] that by FAB mass spectral analysis, the FD formulation of Example 1 which was prepared by the method as stated in [0084] showed a strong signal at m/z =531, which indicates the formation of BME, and that this signal is different from a signal at m/z = 441, which is a signal of glycerol (matrix at the time of analysis) adduct with bortezomib, and that moreover, the an intensity of the signal at m/z = 531 is high enough to distinguish it from the signal at m/z = 441. In view of these matters, it can be deemed that the FD formulation of Example 1 contains a considerable amount of BME.

Therefore, it can be found that the Present Description states that a considerable amount of BME in the state of a lyophilized powder was produced.

B. Demandant TAKATA's assertion

The Demandant TAKATA asserts that it cannot be recognized from the statement of Example 1 that the lyophilized formulation contains a considerable amount of BME, because it is not possible to evaluate whether an amount of a substance which is present in a sample is large or small by size of a peak in FAB mass spectral analysis.

However, as explained in the above (1), it is construed that a rigorous scientific proof is not necessary in order to comply with the support requirement. Thus, in light of the findings concerning the preparation method of a lyophilized product as stated in the above A (including the statements in Exhibit Ko 95 (Written expert opinion by Professor Hei) and Exhibit Ko 96 (Written opinion by Professor Tei) stating that a considerable amount of BME is considered to be produced) and that the strong signal at m/z = 531 is confirmed by FAB mass spectral analysis, it should be deemed that a person ordinarily skilled in the art can reasonably recognize that a considerable amount of the target substance (BME in the state of a lyophilized powder) of the Invention of the Present Compound was produced.

Therefore, the Demandant TAKATA's assertion as mentioned above does not affect the determination in the above A.

(4) Storage stability

A. The Present Description discloses, in [0094] to [0096], test results showing that bortezomib in the state of a solid or a liquid was not stable for longer than 3 to 6 months or longer than 6 months even when stored at a low temperature of 2 to 8°C, whereas in the FD formulation of Example 1 (which contains a considerable amount of BME as mentioned in the above (3)), there was no loss of drug, and no degradation products were produced at any temperature of 5°C, ambient temperature, 37°C, and 50°C for approximately 18 months. According to this statement, it can be deemed that the Present Description states to the extent that a person ordinarily skilled in the art can recognize that the present compound has excellent storage stability as compared to bortezomib.

B. Demandant TAKATA's assertion

The Demandant TAKATA asserts that it is natural to recognize that the improvement in storage stability as stated in [0094] to [0096] of the Present Description was achieved by applying the well-known art of lyophilization using mannitol as an excipient.

In this regard, as asserted, it can be considered that in the FD formulation of Example 1, the total amount of bortezomib used for the preparation did not necessarily result in BME and that bortezomib which was lyophilized with mannitol as an excipient was also contained. Thus, it can be considered that the presence of this lyophilized bortezomib contributes to the improvement of storage stability. However, it can be deemed that recognition by a person ordinarily skilled in the art is to consider that BME also contributes to the improvement of storage stability, since the formulation containing a considerable amount of BME shows storage stability. In addition, no circumstances can be found against this recognition, and it should be acknowledged that only lyophilized bortezomib contributes to the improvement of storage stability.

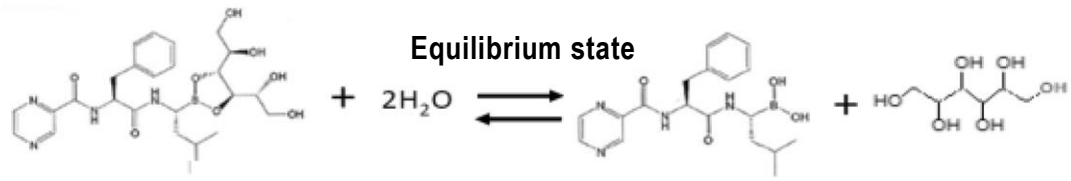
Therefore, since recognition like the above (1) is sufficient for the recognition by a person ordinarily skilled in the art in order to comply with the support requirement, the Demandant TAKATA's assertion as mentioned above does not affect the determination in the above A.

(5) Easiness of dissolution and easiness of hydrolysis

A. The Present Description discloses in [0088] and [0089] that the FD formulation of Example 1 (which contains a considerable amount of BME as mentioned in the above (3)) was completely dissolved in 2 mL of water within 1 to 2 minutes of shaking, the FD formulation of Example 1 was completely dissolved in 1 mL of "propylene glycol:EtOH:H_2O=40:10:50" within 1 minute of shaking, the FD

formulation of Example 1 readily dissolved in 0.9% w/v saline at concentrations up to 6 mg/mL, and in contrast to this, solid bortezomib was not soluble in 0.9% w/v saline at a concentration of 1 mg/mL. According to this statement, it can be deemed that the Present Description states to the extent that a person ordinarily skilled in the art can recognize that the present compound has excellent easiness of dissolution as compared to bortezomib.

In addition, according to the entire import of the oral argument, it can be found that there is common general technical knowledge that an equilibrium state is established between a boronate ester and the corresponding boronic acid by the following equation. Thus, it can be deemed that a person ordinarily skilled in the art can recognize that when the present compound (BME in the state of a lyophilized powder) is dissolved in water, bortezomib is released from BME due to reverse reaction of esterification; that is, the present compound has easiness of hydrolysis.



Incidentally, the Present Description states the result of the proteasome inhibition activity assay which was performed on the FD formulation of Example 1 in order to confirm the easiness of hydrolysis of the present compound in [0090]. However, in view that the specific condition of the assay is not clear and that there are no reliable scientific findings to evaluate whether the observed Ki value of 0.3 nM is due to BME or bortezomib, it cannot be deemed that a person ordinarily skilled in the art can obtain recognition on the easiness of hydrolysis of the present compound on the basis of the above statement.

B. Demandant TAKATA's assertion

The Demandant TAKATA asserts that it is natural to understand that the test results showing the solubility of the FD formulation of Example 1 as stated in [0088] and [0089] of the Present Description were achieved by applying the well-known art of lyophilization using mannitol as an excipient.

However, for the same reason as explained in the above (4)B, the Demandant TAKATA's assertion as mentioned above does not affect the determination in the above A.

C. The Demandant TAKATA's preliminary assertion (the above No. 4, 1(2)B)

The Demandant TAKATA asserts that the statement of the claims of the

Invention of the Present Compound does not specify a particle size of BME, etc., and thus the Patent is claimed beyond the scope where a person ordinarily skilled in the art can understand that the problem can be solved, and therefore the claims violate the support requirement in this regard as well. This assertion is in response to the Patentee's statement that "(In the lyophilization step, BME) precipitates as a fine solid. Therefore, the resulting lyophilized formulation becomes a fine solid (powder), which increases a dissolution rate and consequently improves the reconstitution property" (Patentee's second brief, page 22, lines 3 to 6).

However, the Patentee's statement as mentioned above is a statement that it can explain with scientific rationality the mechanism by which the configuration of the Invention of the Present Compound improves solubility of BME which was subjected to the lyophilizing step. It is construed that this explanation can also be naturally applied to the compound according to the Invention of the Present Compound which is a lyophilized compound. Thus, it cannot be deemed that the Invention of the Present Compound extends the technical scope beyond the scope of the product to which the above mechanism is applied.

Then, it can be deemed that new issues of violation of the support requirement as the Demandant TAKATA asserts do not arise. Therefore, this assertion cannot be accepted.

(6) Specific assertions on technical matters

With regard to whether the Invention of the Present Compound complies with the support requirement, both parties make various assertions as shown in the Attachment, and the results of the court's discussion on these assertions are given in the right column of the Attachment. According to this Attachment, while it is not possible to affirm all of the assertions by the Patentee as is, it can be affirmed that the FD formulation of Example 1 contains a considerable amount of the present compound on the basis of 1(1)a to c and (2)b, the solubility of the present compound can be affirmed mainly on the basis of 2b, the hydrolyzability of the present compound can be affirmed on the basis of 3a, and the storage stability of the present compound can be affirmed on the basis of 4a and b, to the extent that a person ordinarily skilled in the art can reasonably expect. On the other hand, the Demandant TAKATA's assertions are not sufficient to overturn the above findings.

(7) Conclusion

According to the discussions in the above (3) to (6), it should be deemed that the statement of the scope of claims of the Invention of the Present Compound complies with the support requirement, and the trial decision to deny this is erroneous.

2. Reason 1 for Rescission by the Demandant TAKATA (Erroneous determination on the violation of the support requirement for the Invention of the Present Production Method)

(1) Reason 1-1 for Rescission (Erroneous findings on the problem)

The problem of the Invention of the Present Production Method should be found in the same way as that of the Invention of the Present Compound, and it is erroneous for the trial decision to find differently between the two inventions. This is not in dispute between the parties, and the court construes this in the same way.

However, in relation to Reason 5 for Invalidation (Violation of the support requirement (No. 2)), as mentioned in the above 1, the Invention of the Present Compound complies with the support requirement, and the Present Description discloses one example of the preparation method as Example 1 as well. Thus, the Invention of the Present Production Method, which redefines the Invention of the Present Compound in terms of the preparation method in the claims, also complies with the support requirement. Therefore, the erroneous determination on the problem to be solved in the trial decision does not affect the conclusion. The relationship of Reason 2 for Invalidation (Violation of the support requirement (No. 1)) will be discussed in (2) below.

(2) Reason 1-2 for Rescission (Erroneous determination on the scope from which it can be inferred that the problem can be solved)

The Demandant TAKATA asserts that the Invention of the Present Production Method, which does not limit a liquid property, etc. of a mixed solution, violates the support requirement, because even if a person ordinarily skilled in the art can recognize that BME is formed by lyophilizing in the case of the liquid property of the mixed solution as disclosed in Example 1, it cannot be recognized that BME is formed in the case of any other liquid properties similarly.

However, the Present Description discloses in [0068] to [0072] that: the mixed solution contains one or more co-solvents in addition to water, preferably the co-solvent is miscible with water, more preferably the co-solvent is an alcohol including, but not limited to, ethanol and tert-butanol; a range of alcohols in the composition of the solvent mixture and a w/w ratio of a dihydroxy compound (mannitol) to a boronic acid compound (bortezomib) can be adjusted in the specific range; the aqueous mixture can be prepared by any order of addition; and the mixture may further comprise one or more pharmaceutically acceptable excipients, carriers, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the

art. Then, it can be deemed that the method of preparing BME of the Invention of the Present Production Method is not limited to the method as disclosed in Example 1, but includes any methods of preparing BME which a person ordinarily skilled in the art can understand on the basis of Example 1 and other statements of the Present Description and the common general technical knowledge. Thus, there is no deviation between the statement of the scope of claims and the statement of the description.

Therefore, the Demandant TAKATA's assertion as mentioned above cannot be accepted.

(3) For the foregoing reasons, Reason 1 for Rescission by the Demandant TAKATA is groundless.

3. Reason 2 for Rescission by the Demandant TAKATA (Erroneous determination on lack of inventive step (No. 2))

This point relates to a point which was not asserted and determined as a reason for invalidation of the invention of a process in the invalidation trial proceedings. Therefore, normally, the Demandant TAKATA cannot assert this point as reasons for rescinding the portion of the trial decision maintaining the patent on the invention of a process. However, even if the content is discussed just to make sure, the assertion cannot be accepted, as follows.

(1) It can be acknowledged that the findings of Exhibit Ko 1 Invention and the findings of the common feature and the different features by the trial decision are reasonable.

(2) Whether Different Feature 1 would have been easily conceivable

A. Exhibit Ko 1 discloses a boronate ester of the Exhibit Ko 1 Invention, as follows.

(a) As the conventional art, synthesis of N-terminal peptidyl boronic acid esters and acid compounds in general and of specific compounds, has already been stated in documents, and these compounds have been shown to be inhibitors of certain proteolytic enzymes. The problem of the Exhibit Ko 1 Invention is to provide a previously unknown peptidyl boronic acid ester and to provide a method of using the peptidyl boronic acid ester as an inhibitor of proteasome function (page 42, page 45).

(b) The boronate ester of bortezomib is one of the peptidyl boronic acid esters exemplified in the Exhibit Ko 1 Invention (pages 19 and 20 (Claim 51), pages 21 and 22 (Claim 57)).

(c) In a method of inhibiting the growth of a cancer cell, comprising contacting

a cell in need of such inhibiting with an effective growth-inhibiting amount of a compound, boronate esters of bortezomib can be selected as a compound which is a proteasome inhibitor. A boronate ester is obtained by reacting an acid group of a boronic acid with a dihydroxy compound which is preferably selected from pinacol, perfluoropinacol, pinanediol, ethylene glycol, diethylene glycol, 1,2-cyclohexanediol, 1,3-propanediol, 2,3-butanediol, glycerol, and diethanolamine (page 25 (Claim 67), pages 42 to 45, page 58).

B. According to the disclosure in the above A, a boronate ester of bortezomib is exemplified as the peptidyl boronic acid ester which solves the problem of the Exhibit Ko 1 Invention. However, with regard to the dihydroxy compound which reacts with bortezomib to obtain the boronate ester, mannitol is not included in various dihydroxy compounds as exemplified in Exhibit Ko 1 (the above A(c)). Further, in relation to the problem of providing a method of using as an inhibitor of proteasome function, there are no statements in Exhibit Ko 1 suggesting selection of mannitol among numerous dihydroxy compounds which exist in addition to those exemplified in Exhibit Ko 1. Furthermore, it cannot be deemed that such a selection is a matter of common general technical knowledge.

Therefore, it cannot be deemed that it would have been easily conceivable to a person ordinarily skilled in the art to select mannitol as the dihydroxy compound which reacts with bortezomib and to create the configuration of the Present Invention according to Different Feature 1.

(3) Whether Different Feature 2 would have been easily conceivable

In Exhibit Ko 1, "a pharmaceutical composition, comprising a compound according to claims ... 51 ..., or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent" is claimed in Claim 63 (page 25). The compound as claimed in Claim 51 from which Claim 63 depends includes the boronate ester of bortezomib (the above (2)A(b)).

However, even according to Claim 63 as mentioned above, the form which the compound of Exhibit Ko 1 Invention (boronate ester of bortezomib) can take is at most a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent. Exhibit Ko 1 neither discloses nor suggests that the compound of the Exhibit Ko 1 Invention takes the form of a lyophilized powder with a pharmaceutically acceptable carrier. In addition, even if it is a matter of well-known art to lyophilize a compound per se, there is neither disclosure nor suggestion in Exhibit Ko 1 to motivate lyophilizing the compound of Exhibit Ko 1 Invention.

Therefore, it cannot be deemed that it would have been easily conceivable to a

person ordinarily skilled in the art to make the compound of Exhibit Ko 1 Invention (boronate ester of bortezomib) to be in the state of a lyophilized powder.

(4) Demandant TAKATA's assertion

With regard to Different Feature 1, the Demandant TAKATA asserted that BME (ester of bortezomib and mannitol) of the present compound corresponds to a more specific concept of the boronate ester of bortezomib (ester of bortezomib and dihydroxy compound) of the Exhibit Ko 1 Invention. With regard to Different Feature 2, the Demandant TAKATA asserted that the "state of a lyophilized powder" of the present compound is merely one of options of the state which the present compound can take. On the basis of these, the Demandant TAKATA asserts that the Present Invention falls under a selection invention of the Exhibit Ko 1 Invention. On this premise, the Demandant TAKATA asserts that the Present Invention lacks an inventive step.

However, with regard to Different Feature 1, it cannot be deemed that the Exhibit Ko 1 Invention discloses all of numerous compounds which exist conceptually as dihydroxy compounds which are subject to esterification reaction with bortezomib. It is construed that the Exhibit Ko 1 Invention merely discloses, at most, the compounds as exemplified in Exhibit Ko 1 and compounds which can be naturally assumed from the exemplified compounds. Thus, it is clear that mannitol is not included in these dihydroxy compounds. With respect to Different Feature 2, the fact that the compound is in the "state of a lyophilized powder" does not mean that the compound is in a naturally occurring state, but is a result by performing an operation as disclosed in [0084] of the Present Description. Thus, it cannot be deemed that the "state of a lyophilized powder" is one of the options of the state which a substance can take.

Therefore, the Demandant TAKATA's assertion cannot be accepted, because this assertion is erroneous in the premise that the Present Invention falls under a selection invention of the Exhibit Ko 1 Invention.

(5) According to the above, it is not erroneous for the trial decision to determine that it cannot be deemed that the Present Invention lacks an inventive step on the basis of Exhibit Ko 1 Invention as the cited invention.

4. Reason 3 for Rescission by the Demandant TAKATA (Erroneous determination on lack of inventive step (No. 1))

(1) It can be acknowledged that the findings of Exhibit Ko 7 Invention and the findings of the common feature and the different features by the trial decision are

reasonable.

(2) Whether Different Features 1 and 2 would have been easily conceivable

A. Exhibit Ko 7 discloses the following matters.

(a) Bortezomib is a potent inhibitor of 20S proteasome and is proposed as one of anticancer agents (page 758).

(b) Chemical stability of peptide boronic acid derivatives in terms of formulations has not been reported in detail in documents in the past. In attempts to formulate bortezomib for parenteral administration, there have been problems of showing irregular stability behavior and being extremely unstable in specific solvents (page 758).

(c) Bortezomib was susceptible to degradation by oxidation under a large number of experimental conditions, and the degradation was definitely accelerated by peroxide and possibly molecular oxygen (page 765).

B. According to the above disclosure in Exhibit Ko 7, in order to put bortezomib of Exhibit Ko 7 Invention into practical use as a pharmaceutical agent, it is shown that there is a problem of overcoming the chemical instability; i.e., that bortezomib is susceptible to degradation by oxidation. However, there is no disclosure of means or methods, etc. for solving the problem, and moreover, there is neither disclosure nor suggestion with regard to esterification or lyophilization as specific means. Thus, there is no motivation to make the bortezomib of Exhibit Ko 7 Invention to be "BME in the state of a lyophilized powder" of the Present Invention.

Therefore, it cannot be deemed that it would have been easily conceivable to a person ordinarily skilled in the art, who had read the Exhibit Ko 7 Invention, to make the configuration according to Different Features 1 and 2 to be the configuration of the Present Invention.

C. Incidentally, according to each of the evidences of the present case, it can be found as the common general technical knowledge that lyophilization is an advantageous formulation method in terms of stability and solubility. In addition, it can also be found that it is a matter of well-known art to select mannitol as an excipient to be used for lyophilization (it cannot be affirmed that the trial decision did not find these points as matters of common general technical knowledge and well-known art). Then, even though there is neither disclosure nor suggestion with regard to means and methods for solving the problem in Exhibit Ko 7, there is room for construing that it would have been easily conceivable to a person ordinarily skilled in the art to perform formulating of bortezomib per se by lyophilization using mannitol as an excipient on the basis of the general request for a pharmaceutical product to

improve its stability.

However, according to each of the evidences of the present case, it is also common general technical knowledge that lyophilization is performed in order not to change properties of compounds (the findings to the same effect by the trial decision on this point can be affirmed). Thus, to the end, what would have been easily conceivable is "lyophilized 'bortezomib' with mannitol as an excipient", which is a different compound from "'BME' in the state of a lyophilized powder" of the Present Invention.

Therefore, in any case, it cannot be deemed that the Present Invention would have been easily conceivable on the basis of the Exhibit Ko 7 Invention.

(3) Whether the Present Invention would have been easily conceivable in view of the Exhibit Ko 8

The Demandant TAKATA asserts that it would have been easily conceivable to obtain the configuration of the Present Invention by lyophilizing bortezomib in the presence of mannitol, because Exhibit Ko 8 discloses that a boronic acid and mannitol form a complex in a mixed solution and that the mixed solution is subjected to lyophilization to prepare a complex of the boronic acid and mannitol in the form of a lyophilized powder, and it was well known that a complex of a boronic acid and a sugar is in an equilibrium state with an ester in an aqueous solution.

However, Exhibit Ko 8 merely discloses that a lyophilized complex of a boronic acid and mannitol was prepared. Exhibit Ko 8 neither discloses nor suggests the preparation of an ester. Even if it is well known that a complex of a boronic acid and a sugar is in an equilibrium state with an ester in an aqueous solution, Exhibit Ko 8 discloses an invention in which the problem is to prepare a complex in order to increase solubility of a boronic acid (page 3), and this problem is different from the problem suggested by Exhibit Ko 7, which is to increase stability of bortezomib. Thus, there is no motivation to apply the disclosure of Exhibit Ko 8 to the Exhibit Ko 7 Invention.

Therefore, the Demandant TAKATA's assertion as mentioned above does not affect the conclusion that the configuration of the Present Invention would not have been easily conceivable.

(4) According to the above, it is not erroneous for the trial decision to determine that it cannot be deemed that the Invention of the Present Production Method lacks an inventive step on the basis of Exhibit Ko 7 Invention as the cited invention.

5. Conclusion

(1) Among the determinations of the trial decision, it is erroneous to determine that the patent with regard to the Invention of the Present Compound is invalid on the grounds that the invention violates the support requirement. In addition, it is also erroneous for the trial decision to determine that the patent with regard to other Claims (19, 20, 44, and 46) concerning the inventions of a product is invalid in line with this determination.

Therefore, the trial decision shall be rescinded with regard to these Claims.

(2) Among the determinations of the trial decision, it is not erroneous in the conclusion to determine that the request for invalidation of the patent with regard to the Invention of the Present Production Method is groundless in light of all of the reasons for invalidation. In addition, it is also not erroneous for the trial decision to determine that the request for invalidation of the patent with regard to other Claims (38 to 42) concerning the inventions of a process is groundless in line with this determination.

Therefore, the claim by the Demandant TAKATA (the Plaintiff of Case B) shall be dismissed with regard to these Claims.

Intellectual Property High Court, Third Division

Presiding Judge TSURUOKA Toshihiko

Judge UEDA Takuya

Judge ISHIGAMI Yugo is unable to sign and seal because the Judge's post has been changed.

Presiding Judge TSURUOKA Toshihiko

Attachment

The parties' assertions and the court's determinations on technical matters

Note: With regard to the documents (abbreviations) cited in the table which do not show evidence numbers, the relationships with the evidence numbers in the present case are as follows.

Written opinion Hei	Exhibit Ko 95
Written opinion Tei	Exhibit Ko 96
Bo	Exhibit Otsu 2
Written opinion Ki	Exhibit Otsu 6
Experiment Kou 1	Exhibit Ko 52
Experiment Kou 3	Exhibit Ko 54
National Publication of International Patent Application No. 245	Exhibit Ko 1

1. Whether a person ordinarily skilled in the art as of the priority date of the present case, who has read the Present Description, can understand that the FD formulation of Example 1 contains a considerable amount of the present compound

(1) From the content of the lyophilization step (the Present Description [0084])

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
a	From the statement in [0040], it is possible to understand the outline of the reaction mechanism by which BME is obtained from Bz.			From the statement in [0040], a person ordinarily skilled in the art can understand that BME is obtained by the esterification reaction of Bz.

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
b	Under the condition as stated in [0084], it can be understood that a considerable amount of BME is produced in the step of preparing the mixed solution (Written opinion Hei, Written opinion Tei).	It cannot be easily predicted even by experts without experimentation that a considerable amount of BME is produced under the condition of [0084].		Taking into consideration the incorporation of the sugar moiety at the initial stage of the synthesis in [0066], and the equilibrium between Bz and BME in [0082] as well as FAB, it can be considered that it can be reasonably expected that a considerable amount of BME will be produced under the condition of [0084].
c	Even written opinion Ki submitted by the Demandant TAKATA acknowledges that the conditions of mixing and stirring in [0084] are preferable for the esterification of Bz.	Written opinion Ki only states that the conditions of mixing and stirring in [0084] increase a rate of the esterification. Written opinion Ki states that it is unclear whether the equilibrium of esterification will shift toward Bz (non-ester) or toward BME (ester) under these conditions.		In light of the equilibrium equation of Bz and BME in [0082], it can be deemed that the presence of tert-butanol reduces an amount of water and thus the equilibrium will shift toward the formation of BME.

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
d	The lyophilizing step is further divided into a freezing step and a drying step, and the esterification reaction also proceeds during the freezing step when solvents such as water are removed as ice crystals (Written opinion Tei).	The Patentee's assertion lacks an objective basis. In the freezing step at a very low temperature, a solution assumes the state of a solid. Under such a condition, it is considered that the esterification reaction hardly proceeds (Written opinion Ki), and there is no common general technical knowledge that the esterification reaction will proceed.		It is considered that the esterification proceeds under tert-butanol and heating prior to lyophilization, and that the esterification hardly proceeds during lyophilization.

(2) From the results of FAB mass spectral analysis [0086]

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
b	The result of FAB mass spectral analysis of the lyophilized product showed a strong signal at m/z = 531 which indicates the formation of BME (the first half of paragraph [0086]). From this fact, it is understood that a considerable amount of BME is produced in the lyophilized formulation.	FAB mass spectral analysis is a qualitative analysis method, and it is not possible to evaluate whether an amount of a substance which is present is large or small by size of a peak (Written opinion Ki).		An amount of produced BME is not known from FAB alone. However, taking into consideration the incorporation of the sugar moiety at the initial stage of the synthesis in [0066], the equilibrium between Bz and BME in [0082], and the condition of [0084] as well as a measurable amount of FAB, it can be acknowledged that a considerable amount will be produced.

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
c	Molecular ionic strength of ester compounds is usually very low (Bo) and nevertheless, FAB mass spectral analysis showed a strong signal of BME. Therefore, it is understood that a large amount of BME was produced.	It is not proven that the discussion in Bo is common general technical knowledge which can be applied to BME. The second half of paragraph [0086] states that BME is chemically stable. Thus, when a person ordinarily skilled in the art reads in combination with this, the person would not consider that the molecular ionic strength of BME is low. Therefore, a person ordinarily skilled in the art cannot arrive at the understanding as mentioned on the left.		From the point of the molecular ionic strength of BME, it is not possible to obtain any findings on an amount of BME which is present.
d		The signal of the glycerol adduct with Bz (m/z = 441) was very low as compared to the signal of BME (m/z = 531) (the second half of paragraph [0086]). This merely shows chemical stability of BME in the sense that BME will not fragment during an ionization step, and is irrelevant to an amount of produced BME (Written opinion Ki).		The signal at m/z = 441 shows the reaction of Bz with a solvent glycerol during FAB measurement. Therefore, it can be deemed that the signal is irrelevant to an amount of produced BME.

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court

2. Whether a person ordinarily skilled in the art as of the priority date of the present case, who has read the Present Description, can understand that the excellent solubility of the FD formulation of Example 1 as shown in Example 3 is due to the present compound

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
b	It can be understood on the basis of the common general technical knowledge that BME has a high acidity and thus easily produces a BME ion to dissolve (Written opinion Tei).	There is no objective evidence to support the opinion of written opinion Tei, and this opinion cannot be deemed to be common general technical knowledge.		Although there is no other evidence to support written opinion Tei, this opinion is consistent with the chemical structure of BME. Therefore, it can be deemed that written opinion Tei is one piece of the evidence to support the Patentee's assertion.

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
c	Because BME has more hydroxyl groups than Bz, BME exhibits excellent solubility, maintains the solution state for a longer period of time in the freezing step, and precipitates as a solid while maintaining dispersibility. Thus, BME precipitates as a fine solid in a lyophilized formulation and exhibits high solubility when dissolved in water again. In contrast thereto, Bz has poor solubility. Thus, when a solution is concentrated during the freezing step, Bz cannot maintain the solution state at an early stage. Therefore, Bz precipitates as a solid all at once, resulting in agglomeration (Written opinion Hei).	(1) Solubility is not determined only by the number of hydroxyl groups. (2) If it is essential for the solubility that BME exists in the form of a fine solid, then the Invention of the Present Compound, which does not specify that the BME is in such form, violates the support requirement, because the invention claims a right beyond the scope where it can be recognized that the problem can be solved.		(1) With regard to the solubility, although there is no other evidence to support written opinion Hei, this opinion is consistent with the chemical structures of BME and Bz. Thus, it is sufficient to affirm this opinion. (2) However, with regard to how difference in the solubility leads to the precipitation of solids, the explanation in written opinion Hei tends not to fully consider the condition of Example 1 (such as the presence of tert-butanol).

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
d	From Experiments Kou 1 and 3, it can be understood that the excellent solubility of the lyophilized formulation is due to BME.	Compliance with the support requirement should not be affirmed by additional experiments on or after the filing date of the patent application. In order to draw the conclusion as asserted on the left, it is essential that Experiments Kou 1 and 3 be control experiments between BME of the Invention of the present compound and the lyophilized formulation of Bz with mannitol, which is not esterified. However, Experiments Kou 1 and 3 are not such experiments.		Experiments Kou 1 and 3 compared [i] a mere mixed powder of Bz and mannitol and [ii] a lyophilized product such as Bz and trehalose, etc., both of which show whether solubility is high or low in different systems. Therefore, these experiments do not provide information on the difference in solubility between Bz and BME in the state of a lyophilized powder.

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
e	Solubility is different from a dissolution rate. In light of the mechanism of lyophilization, the solubility of Bz is not improved simply by lyophilizing with mannitol. It is understood that the excellent solubility of the FD formulation of Example 1 is due to BME having excellent solubility.			Notwithstanding the difference between the solubility and the dissolution rate, it is not possible to deny that a considerable amount of BME is produced, as mentioned in 1(2)b. Therefore, it is possible to recognize that the solubility is derived from BME.

3. Whether a person ordinarily skilled in the art as of the priority date of the present case, who has read the Present Description, can recognize that the present compound has excellent hydrolyzability

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
a	[0082] clearly states that "upon reconstitution in an aqueous medium, an equilibrium is established between any boronate ester present in the composition and the corresponding boronic acid. Typically, the equilibrium is reached quickly, e.g., within 10 to 15 minutes, after the addition of water."			A person ordinarily skilled in the art understands factors of esterification and hydrolysis from an equilibrium between a boronic acid ester and a boronic acid in [0082], and recognizes that since these are not irreversible reactions, if a combined compound has been formed by esterification, the equilibrium can also be induced in the direction of hydrolysis.

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
b	The Ki value (0.3 nM) of the FD formulation of Example 1 in the proteasome inhibition assay in [0090] was the same as that of Bz. From this fact, a person ordinarily skilled in the art can understand that BME has excellent hydrolyzability. The Demandant TAKATA's assertions (1) and (3)[i] merely point out probability and possibility, and are not supported by evidence. With regard to the Demandant TAKATA's assertion (2), Ki value is determined by an assay, and therefore can vary depending on documents.	(1) The assertion as mentioned on the left premises that BME does not have Pa inhibitory activity. However, this premise is not proven and is not common general technical knowledge. On the contrary, as of the priority date of the present case, it was known that not only a peptidyl boronic acid but also its sugar esters have Pa inhibitory activity, and that the sugar esters may show higher activity (National Publication of International Patent Application No. 245, page 44, page 119 Table II; Iqbal [Exhibit Otsu 5], page 287) (Brief, (2), page 17). (2) Other publicly known documents (Adams [Exhibit Ko 64], Teicher [Exhibit Ko 65]) state that the Ki value of Bz is 0.6 nM. Therefore, it cannot be understood that the Ki value of 0.3 nM measured in [0090] is a value of Bz.		In the first place, it is difficult to discuss hydrolyzability in terms of Ki values, because the equilibrium state under the assay condition is unclear from the statement of the Present Description.

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
		(3) The results of [0090] are also consistent with a plurality of the following possibilities. [i] BME did not hydrolyze, but it has Pa-inhibitory activity as shown in the above (1). Thus, the Ki value as mentioned on the left was shown. [ii] The FD formulation of Example 1 also contained a considerable amount of Bz which was not esterified, and this Bz showed the Ki value as mentioned on the left. (4) In view of the formula for calculating a Ki value (Rock [Exhibit Ko 61]), the Ki value from the assay in [0090] is a Ki value of a mixed solution of BME and Bz in the equilibrium state and cannot be considered a Ki value of released Bz.		

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court
d	From the statement in [0082] concerning the equilibrium between BME and Bz, it is understood that BME easily hydrolyzes. It is common general knowledge of chemical equilibrium that the equilibrium shifts toward esterification under the condition of preparing the solution (adding tert-butanol and heating at 40°C), whereas the equilibrium shifts toward Bz under the condition of reconstituting (water at room temperature).			In view of the equilibrium in [0082], it is possible that when preparing and reconstituting BME, the equilibrium may shift either [i] toward the direction of BME formation by esterification or [ii] toward the direction of Bz formation by hydrolysis, due to differences in the conditions such as adding tert-butanol and heating at 40°C, etc.

4. Whether a person ordinarily skilled in the art as of the priority date of the present case, who has read the Present Description, can understand from the statement of Example 5 that the present compound has storage stability

	Patentee's assertion	Demandant TAKATA's assertion		Judgment of this court

a	From the statement in [0094] to [0096], a person ordinarily skilled in the art can understand that the Invention of the present compound (BME in the form of a lyophilized powder) has excellent storage stability.	[0094] to [0096] show that the FD formulation of Example 1 has excellent storage stability. However, a person ordinarily skilled in the art cannot understand that the FD formulation of Example 1 contains a considerable amount of BME (the above 1). Therefore, a person ordinarily skilled in the art cannot also understand that the storage stability is due to BME.		Even though BME is not isolated, it can be reasonably expected that a considerable amount of BME will be produced, as mentioned in 1(2)b. Therefore, it can be understood that the stability is derived from BME.
b	In BME, the boronic acid portion of Bz is protected by esterification, which increases stability (Written opinion Hei, written opinion Tei).			Although there is no other evidence to support written opinions Hei and Tei, this is a reasonable inference in view of the chemical structure.

c	Mannitol in a lyophilized formulation exists in the (vitrified) amorphous state. Therefore, the oxidative decomposition of Bz cannot be prevented (Written opinion Hei).			Notwithstanding the state of mannitol, it is not well known that mannitol as an excipient stabilizes Bz.
d	From Experiments Kou 1 and 3, it can be understood that the excellent storage stability of the lyophilized formulation is due to BME.	Compliance with the support requirement should not be affirmed by additional experiments on or after the filing date of the patent application. In order to draw the conclusion as asserted on the left, it is essential that Experiments Kou 1 and 3 be control experiments between BME of the Invention of the Present Compound and the lyophilized formulation of Bz with mannitol, which is not esterified. However, Experiments Kou 1 and 3 are not such experiments.		In order for the lyophilized formulation of Bz with mannitol, which is not esterified, to be used as a comparative example, adjusting an amount of tert-butanol in Example 1 is considered. As mentioned in the above 2d, Experiments Kou 1 and 3 compared [i] a mere mixed powder of Bz and mannitol and [ii] a lyophilized product such as Bz and trehalose, etc., both of which merely evaluate whether stability is high or low in different systems. Therefore, these experiments do not provide information on whether the stabilities of Bz and BME are high or low.