Advisory Opinion

Advisory Opinion No. 2015-600023

Chiba, Japan	
Demandant	YAMADA, Takahiro
Tokyo, Japan	
Patent Attorney	Ono International Patent Firm
USA	
Demandee	ELI LILLY JAPAN K.K.
Tokyo, Japan	
Patent Attorney	KOBAYASHI, Hiroshi
Tokyo, Japan	
Patent Attorney	HINO, Mami
Tokyo, Japan	
Patent Attorney	KATO, Shimako
Tokyo, Japan	
Patent Attorney	TAMURA, Kyoko

The advisory opinion on the technical scope of the patent invention of Japanese Patent No. 2860071 is stated and concluded as follows:

Conclusion

"The crystal of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride" indicated in the explanatory document of Article A does NOT fall within the technical scope of the invention of Japanese Patent No. 2860071.

Reason

1 History of the procedures

Japanese Patent No. 2860071 is based on an patent application filed on September 18, 1995 (claiming priority dates under the Paris Convention of September 19, 1994 and April 26, 1995, United States) and the establishment of patent right was registered on December 4, 1998 (the number of claims: 7).

The request for the advisory opinion was filed on July 30, 2015 by Takahiro YAMADA (hereinafter referred to as "Demandant"). Then, Patentee (hereinafter referred to as "Demandee") submitted a written reply on October 23, 2015, and the body sent Demandant an Inquiry dated November 30, 2015, and Demandant submitted a reply dated December 18, 2015 although Demandant did not submit a written refutation in response to the written reply made by Demandee, and then, Demandee submitted another written reply (hereinafter referred to as "second written reply") on March 18, 2016.

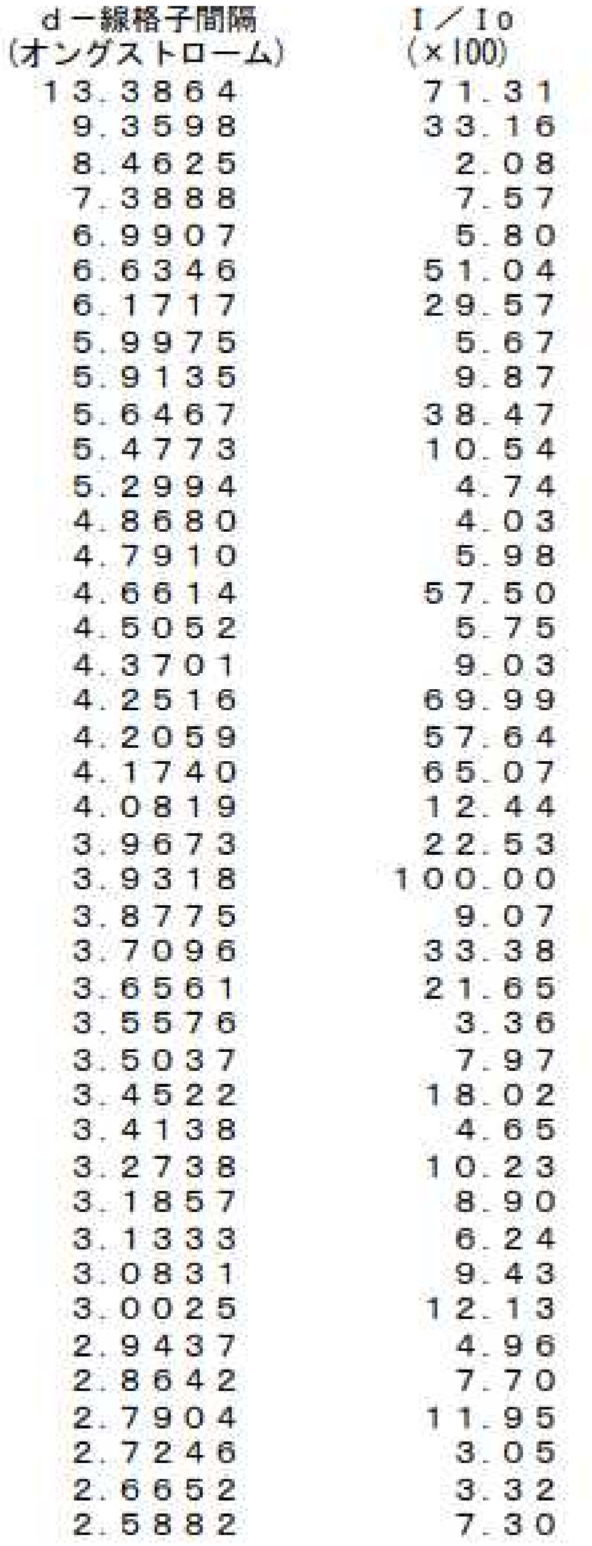
2 The object of the demand

The object of the demand is to request an advisory opinion to the effect that "The crystal of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride" indicated in the explanatory document of Article A does NOT fall within the technical scope of the invention of Japanese Patent No. 2860071.

3 The patent Invention

The Invention of Japanese Patent No. 2860071 should be specified in the matters recited in Claims 1 to 7 of the Claims in view of the description and the claims attached to the application. The constituent components of the Invention according to Claim 1 (hereinafter referred to as "the patent Invention 1") are separately described as follows: For convenience, the constituent components are denoted by the symbols A to C.

"A. substantially showing the following X-ray diffraction pattern obtained by a Cu irradiation beam:



dー線格子間隔（オングストローム）	I／Io（×100）
13.3864	71.31
9.3598	33.16
8.4625	2.08
7.3888	7.57
6.9907	5.80
6.6346	51.04
6.1717	29.57
5.9975	5.67
5.9135	9.87
5.6467	38.47
5.4773	10.54
5.2994	4.74
4.8680	4.03
4.7910	5.98
4.6614	57.50
4.5052	5.75
4.3701	9.03
4.2516	69.99
4.2059	57.64
4.1740	65.07
4.0819	12.44
3.9673	22.53
3.9318	100.00
3.8775	9.07
3.7096	33.38
3.6561	21.65
3.5576	3.36
3.5037	7.97
3.4522	18.02
3.4138	4.65
3.2738	10.23
3.1857	8.90
3.1333	6.24
3.0831	9.43
3.0025	12.13
2.9437	4.96
2.8642	7.70
2.7904	11.95
2.7246	3.05
2.6652	3.32
2.5882	7.30

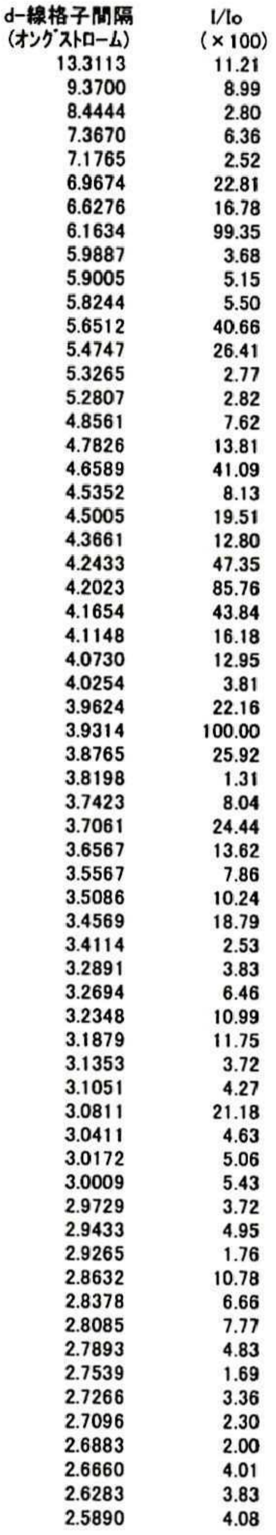
dー線格子間隔（オングストローム） d-line grating space (angstroms)

B. A non-solvated crystal form of
C.
6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt."

4 Article A

Article A includes the constituent components of the following a to c according to the explanatory document of Article A and Exhibit Ko #6 (the Experimental report prepared by Osamu Okamoto of Ryoto Fine Co., Ltd. dated December 14, 2015) (hereinafter Exhibit Ko #6 is referred to as " Ko-6", and the other evidence is referred to similarly), which were submitted by the Demandant:

"a. showing the following X-ray diffraction pattern obtained by a Cu irradiation beam:



d−線格子間隔 (オングストローム)	I/Io (×100)
13.3113	11.21
9.3700	8.99
8.4444	2.80
7.3670	6.36
7.1765	2.52
6.9674	22.81
6.6276	16.78
6.1634	99.35
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3.7061	24.44
3.6567	13.62
3.5567	7.86
3.5086	10.24
3.4569	18.79
3.4114	2.53
3.2891	3.83
3.2694	6.46
3.2348	10.99
3.1879	11.75
3.1353	3.72
3.1051	4.27
3.0811	21.18
3.0411	4.63
3.0172	5.06
3.0009	5.43
2.9729	3.72
2.9433	4.95
2.9265	1.76
2.8632	10.78
2.8378	6.66
2.8085	7.77
2.7893	4.83
2.7539	1.69
2.7266	3.36
2.7096	2.30
2.6883	2.00
2.6660	4.01
2.6283	3.83
2.5890	4.08

d ー線格子間隔（オングストローム）	d-line grating space (angstroms)

b. A non-solvated crystal form of
c.
6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt,"

5 Allegations of the parties
(1) Demandant

The Demandant argues that Article A does not fall within the technical scope of the patent Invention since the constituent components A is not found in the Article A while the constituent components B and C are found there.

(2) Demandee

The Demandee argues substantially as follows.

(i) Although the Demandant insists in the written request for advisory opinion that he has requested this advisory opinion to prevent any future dispute with respect to the sales project of pharmaceutical formulation using the crystal of Article A, the method described in the explanatory document of Article A is a manufacturing method of only 121g for a prototype at a laboratory stage, which is not an appropriate manufacturing method of crystal used for "the sales of pharmaceutical formulation." Thus, the request for advisory opinion may not achieve the above goal nor have a legal interest of the request. Therefore, the request for advisory opinion should be rejected. (see the written reply, pages 2 to 4)

(ii) Whether or not the constituent components are found in Article A may be determined in accordance with the description of page 1, line 2 to page 2, line 3 in the explanatory document of Article A and the appendant powder X-ray diffraction measurement condition on page 3. Since the manufacturing method described in the explanatory document of Article A is what is disclosed in Examples 18 and 20 of Ko-1 (Japanese Unexamined Patent Application Publication No. 57-181081), it is not appropriate for the manufacturing method of Article A and it cannot be a basis for determining whether or not the constituent components are found in Article A. (see the written reply, page 5)

(iii) 2θs of Article A are identical to θs calculated from d recited in the constituent component A within a margin of ±0.2°. Thus, the constituent component A is found in Article A. It is not required to identity the crystal that the relative intensity I/I_0 falls within 20%. (see the written reply, pages 6 to 10)

(iv) All the constituent components A to C are found in Article A although Demandant insists that Article A does not fall within the technical scope equivalent to the Invention, Thus, it is not necessary to examine whether the requirements of the doctrine of equivalence in this case are met or not. Although Demandant insists that regarding Article A, the first, fourth, and fifth requirements of the doctrine of equivalence are not met, but such argument is incorrect as set forth below.

Relative Intensity I/I_0 is not an essential part of the Invention and thus the first requirement is met.

The manufacturing method described in the explanatory document of Article A (Examples 18 and 20 of Ko-1) is not an appropriate manufacturing method of Article A. Thus, Article A is not identical to or easily conceivable on the basis of publicly known technique. Thus the fourth requirement is met.

The manufacturing method described in the explanatory document of Article A (Id.) is not an appropriate manufacturing method for Article A. Thus, this is not excluded intentionally from the technical scope of the Invention. There is no reason to find that what is manufactured by use of aluminum chloride as an acylation catalyst is intentionally excluded from the technical scope of the Invention. Thus, the fifth requirement is met. (see the written reply, pages 10 to 13)

(v) Since the manufacturing method described in the explanatory document of Article A differs from that of the experiment of Ko-6 in the experimental condition, it cannot be proved that the crystal of Article A has really existed in accordance with the experiment of Ko-6. That is, it cannot be said that Article A has really existed. (see the second written reply, pages 2 to 5)

6 Comparison / Judgment

(1) The patent Invention 1

A Undisputed matter

Article A is compared to the patent Invention 1 from the viewpoint of the constituent components A to C. Components A and B are found in Article A since "6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt" of the constitution c and "A non-solvated crystal form" of the constitution b correspond to "6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt" of the constituent component C and "A non-solvated crystal form of" the constituent component B, respectively.

It is thus recognized that the constituent components B and C are found in Article A of the patent Invention 1 from the viewpoint of the constitutions b and c.

In this respect, there is no dispute between the parties.

B The disputed matter (the constituent component A)

(A) There is a dispute between parties as to whether the constituent component A of the patent Invention 1 is found in Article A.

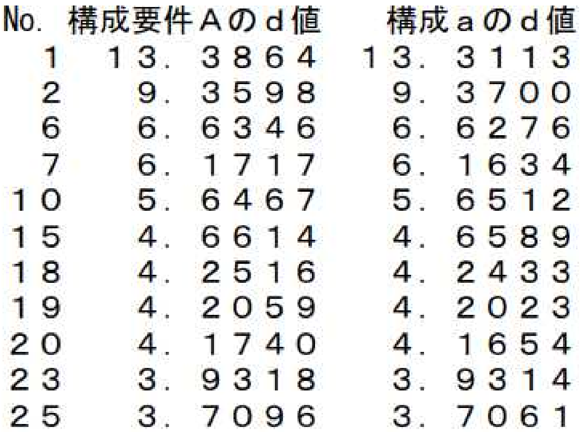
Demandant argues that "In connection with the constituent component A of 'substantially showing ... the following X-ray diffraction pattern obtained by Cu irradiation beam', "substantially showing" is construed as meaning that, in the combination of the numerals of forty-one d-line grating spaces (hereinafter referred to as 'd value'.) and the numerals of the relative intensity I/I_0, the margin of 2θ, which is associated with d value via Bragg equation ($\lambda=2d\sin\theta$, λ is CuKα line of 1.5418Å), falls within 0.20° and the margin of relative intensity I/I_0 falls within 20% at a maximum. The crystal of the patent Invention and the crystal of Article A are significantly different in the relative intensity I/I_0 of X-ray diffraction peak. Thus, the constituent component A is not found in Article A ". (see the written request for advisory opinion, pages 5 to 8)

In contrast, Demandee argues that "all the 2θs of Article A are identical to 2θs calculated from d value of the constituent component A with a margin of ±0.2°. Further, the requirement for crystal identity depends on only the margin of diffraction angle 2θ of ±0.2°, which can be understood according to Otsu-2 (Sixteenth revision, Japanese Pharmacopoeia, March 24, 2011, by Ministerial Notification No. 65 of MHLW), Ko-4 (US Pharmacopeia, 1990, pp. 1621-1623), Otsu-3(Katsumi OHNO, Akira KAWASE, Toshihiro NAKAMURA, "X-ray analysis", first impression of the first edition, Kyoritsu Publishing, May 25, 1987, pp. 52-55). Demandee argues that therefore Article A is considered to be identical to the crystal of the patent Invention 1 and thus the constituent component A is found in Article A." (see the written reply, pages 6 to 9)

The body examines whether or not the constituent component A is found in Article A as follows.

(B) First, the body examines whether or not forty-one d values of the constituent component A are identical to d values in the constitution a (amounts to 62.). The forty-one d-values of the constituent component A are numerals with the number of four decimals, and are described with a unit angstrom (Advisory opinion's note: denoted as Å. 1Å is 10^{-10}m) and associated with diffraction angle 2θ measured by an X-ray diffraction experiment via Bragg's equation mentioned above ($\lambda=2d\sin\theta$, λ is CuKα line of 1.5418Å) and represent lattice spacing in a crystal.

The forty-one d-values of the constituent component A and the d-values in the constitution a have certain values close to each other. Therefore, for example, eleven d-values with large relative intensity in the constituent component A and d-values closest to them in the constitution a are put in a row in the following ("No." was numbered from 1 to 41 in the order they are shown.).



No.	構成要件Ａのｄ値	構成ａのｄ値
１	１３．３８６４	１３．３１１３
２	９．３５９８	９．３７００
６	６．６３４６	６．６２７６
７	６．１７１７	６．１６３４
１０	５．６４６７	５．６５１２
１５	４．６６１４	４．６５８９
１８	４．２５１６	４．２４３３
１９	４．２０５９	４．２０２３
２０	４．１７４０	４．１６５４
２３	３．９３１８	３．９３１４
２５	３．７０９６	３．７０６１

構成要件Ａのｄ値	d-values of the constituent component A
構成ａのｄ値	d-values of the constitution a

Regarding the above d values, none of d-values in the constituent component A is identical to any of d-values in the constitution a to four decimals places.

Further, since Demandant uses numerals of 2θs which are associated with d-values, eleven 2θs with large relative intensity in the constituent component A and the corresponding eleven 2θs in the constitution a are shown as follows.

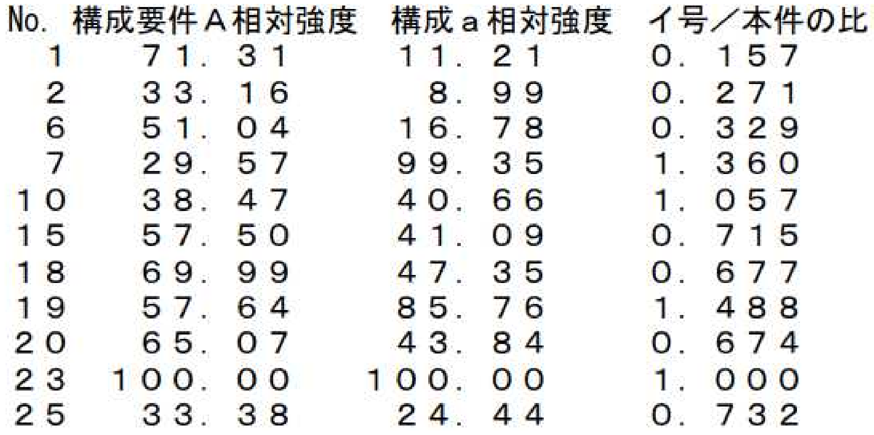
No.	構成要件Ａ対応２θ	構成ａ対応２θ
１	６．６０	６．６４
２	９．４５	９．４４
６	１３．３４	１３．３６
７	１４．３５	１４．３７
１０	１５．６９	１５．６８
１５	１９．０４	１９．０５
１８	２０．８９	２０．９３
１９	２１．１２	２１．１４
２０	２１．２９	２１．３３

２３	２２．６１	２２．６２
２５	２３．９９	２４．０１

構成要件Ａ対応２θ	2θ corresponding to the constituent component A
構成ａ対応２θ	2θ corresponding to the constitution a

Since the description fails to teach resolution of 2θ in X-ray diffraction measurement, the values of 2θ cannot be to two decimals and they may be inaccurate. Regarding the above calculated values of 2θ to two decimals, none of those of the constituent component A is identical to any of those of the constitution a. Further, the description of patent Invention does not teach that the above d-values or the numerals of the diffraction angle 2θ for calculating the d-values may have an allowable margin for error.

(C) Relative intensity corresponding to the above eleven d-values is shown in a row as below:



No.	構成要件Ａ相対強度	構成ａ相対強度	イ号／本件の比
1	７１．３１	１１．２１	０．１５７
2	３３．１６	８．９９	０．２７１
6	５１．０４	１６．７８	０．３２９
7	２９．５７	９９．３５	１．３６０
１０	３８．４７	４０．６６	１．０５７
１５	５７．５０	４１．０９	０．７１５
１８	６９．９９	４７．３５	０．６７７
１９	５７．６４	８５．７６	１．４８８
２０	６５．０７	４３．８４	０．６７４
２３	１００．００	１００．００	１．０００
２５	３３．３８	２４．４４	０．７３２

構成要件Ａ相対強度	The constituent component A relative intensity
構成ａ相対強度	The constitution a relative intensity
イ号／本件の比	A ratio of Article A/the Invention

Regarding the above relative intensities, in the viewpoint of only the eleven peaks with large intensity in the constituent component A, the relative intensities of the peaks therein show a completely different pattern from the relative intensities of the corresponding peaks in the constitution a.

Moreover, the description does not teach that relative intensity may have a certain amount of margin for error with respect to the forty-one peaks including the above eleven peaks. Further, there is no hint in the description to suggest that the crystal of the patent Invention 1 may be identified without regard to relative intensity.

(D) In powder X-ray diffraction measurement, the same crystal does not always provide the same diffraction angle nor the same relative intensity of peak, due to the measurement error of a device for the use in the measurement or the status of sample for the measurement. In a patent application where a crystal is identified by, e.g., diffraction angle, the margins for diffraction angle and relative intensity recited in the claims may fail to be determined uniformly. In some patent applications, diffraction angle 2θ has no margin, but only a series of numerical values are described. In the other applications, the margin is set to ±0.1 or ±0.2. If a crystal is specified by d-value instead of diffraction angle 2θ, given a constant allowable margin of error for 2θ, the allowable margin of error for d-value calculated therefrom may be different between a region of large d-value and a region of small d-value. Moreover, it is supposed that measurement error of d-value gets smaller and more accurate as the diffraction angle gets closer to 180° (Otsu-3). In view of these facts, with respect to the patent Invention 1 reciting the combinations of forty-one d-values and relative intensity I/I_0 as the constituent component A, the recitation of "substantially showing ... the following X-ray diffraction pattern" is not a sufficient requirement to consider numerical variations due to measurement errors for the patent Invention where the claims and the description fail to describe allowable margin for d-value (or diffraction angle) and a specific range of the allowable error, because it cannot be uniformly determined as to whether or not any article falls within a technical scope (see rendition of judgment on January 27, 2015, the determination of Heisei 25-nen(wa) No. 33993 and rendition of judgment on December 24, 2015, the determination of Heisei 27-nen(ne) No. 10031). Further, if you consider the following facts: there is a difference of relative intensity in the above (iii), and the relative intensity is an amount dependent of the existing amount of lattice spacing with a specific dimension in a crystal, and the difference between the relative intensity of the constitution a in Article A and the relative intensity of the constituent component A is supposed to be indicative of the difference in the ratio of the existing amount of a specific size of lattice spacing between crystals; the difference of relative intensity in the above (iii) becomes greater as the whole aspect of X-ray diffraction pattern differs; and the patent was granted by reciting forty-one d-values and relative intensity thereof.

Accordingly, since there are the differences among d-values as mentioned above

(ii) and the differences of relative intensity as mentioned above (iii), it is not recognized that the constituent component A in the patent Invention 1 is not found in Article A.

C Examination regarding application of the doctrine of equivalence

The combinations of forty-one d-values and relative intensity thereof in the patent Invention 1 are the essential constituent components of the Invention.

Further, according to the description, the conventional raloxifene hydrochloride had defects of contamination of chlorobenzene or aluminum contaminates that is due to aluminum chloride catalyst or thioester coproduct that are difficult to purify and unpleasant thiol odor. The novel synthetic method provides a novel non-solvated crystal form of raloxifene free from chlorobenzene and aluminum contaminates and substantially odor-free (Paragraphs [0001] to [0009]). The manufacturing method is intended to obtain a specific crystal through the acylation with an acylating agent in the presence of BX3 (X is chloro or bromo) (Paragraphs [0010] to [0011]). The patent Invention 1 is a resultant specific crystal different from the conventional technique. It is recognized that the combinations of the above forty-one d-values and relative intensity thereof are the essential constituent components for the identification of the crystal.

Accordingly, the constituent component A is an essential part of the patent Invention.

Therefore, without examining other requirements of the doctrine of equivalence, it cannot be recognized that Article A is equivalent to the patent Invention 1.

(2) Regarding the inventions according to Claims 2 to 7

These inventions include the constituent components A to C. As is described in the above (1), it cannot be recognized that the constituent component A is found in Article A.

7 Allegations of the parties

Demandee's argument about the above item 5(2) is examined in the following:

Regarding the point (i)

The sales project is not necessarily the actual one for the request of advisory opinion. Indeed, the production scale of Article A is at a laboratory stage, but the request for advisory opinion cannot be unallowable. Further, Ko-6 shows that Article A actually exists. Accordingly, Demandee's argument to the effect that the request for the advisory opinion should be rejected is not affirmed.

Regarding the point (ii)

The body has also determined the sufficiency of the constituent component for Article A on the basis of the description of page 1, line 2 to page 2, line 3 of the explanatory document of Article A accompanied by the powder X-ray diffraction measurement condition on page 3.

Regarding the point (iii)

The sufficiency of the constituent component A has been examined as in the above item 6(1)ii.

Regarding the point (iv)

The doctrine of equivalence has been examined as in the above item 6(1)iii.

Regarding the point (v)

Even if there is a minor difference between the manufacturing method described in the explanatory document of Article A and the experimental condition of Ko-6, it can be seen from the description of the experimental procedure and the experimental results of Ko-6 that "a non-solvated crystal form of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt showing the following X-ray diffraction pattern obtained by Cu irradiation beam" described in the explanatory document of Article A and a non-solvated crystal form of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt with the combinations of forty-one d-values and relative intensity I/I0 identical to those of the Article A down to four decimals places and two decimals places respectively are actually present. Thus, Demandee's argument is not affirmed.

8 Closing Remarks

For the above reasons, at least the constituent component A of the patent Invention 1 is not found in Article A. Therefore, it does not fall within the technical scope of the patent Invention.

Accordingly, the advisory opinion shall be made as described in the Conclusion.

April 19, 2016

Chief administrative judge: INOUE, Masahiro
Administrative judge: NAKATA, Toshiko

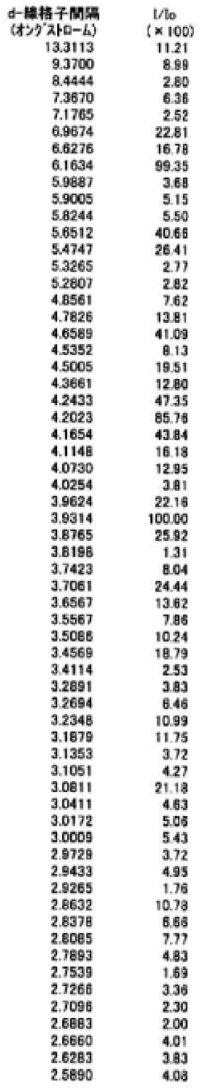
Administrative judge: TOMINAGA, Tamotsu

<Explanation of Article A>

Hereinafter, the explanatory document of Article A and Ko-6 of Demandant's submission are attached. Ko-6 was submitted for the purpose of establishing the fact that a non-solvated crystal form of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt with a X-ray diffraction pattern described in the explanatory document of Article A was actually present.

Explanatory document of Article A

Article A is a non-solvated crystal form of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt showing the following X-ray diffraction pattern obtained by Cu irradiation beam:



d-線格子間隔 (ｵﾝｸﾞｽﾄﾛｰﾑ)	I/Io (× 100)
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3.8196	1.31
3.7423	8.04
3.7061	24.44
3.6567	13.62
3.5567	7.86
3.5086	10.24
3.4569	18.79
3.4114	2.53
3.2891	3.83
3.2694	6.46
3.2348	10.99
3.1879	11.75
3.1353	3.72
3.1051	4.27
3.0811	21.18
3.0411	4.63
3.0172	5.06
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2.6883	2.00
2.6660	4.01
2.6283	3.83
2.5890	4.08

ｄ－線格子間隔（オングストローム）	d-line grating space (angstroms)

The manufacturing method and the measurement condition of powder X-ray diffraction are set forth below:

(Manufacturing method)

Article A is manufactured by the manufacturing method described in Examples 18 and 20 of Japanese Unexamined Patent Application Publication No.57-181081 as shown below, and aluminum chloride is used as an acylation catalyst.

A liquid mixture consisting of 1.5g of 4-(2-pyperidinoethoxy)benzoic acid hydrochloride, 20 ml of chlorobenzene, 3 ml of thionyl chloride, and 2 drops of dimethylformamide was stirred for 2 hours at 75 to 79°C to prepare the corresponding acid chloride and the temperature was lowered to 65°C in a depressurized condition. Distillation continued until the pot temperature reached 90°C, and after the addition of 20 ml chlorobenzene, distillation was performed again (until the pot temperature reached 90°C) and then cooled. To the liquid mixture there were added 15 ml of dichloromethane, 1.35 g of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene, 5 g of aluminum chloride, and 15 ml of dichloromethane and then the resultant mixture was stirred for 90 minutes at 27 to 29°C. Thereafter, 1.6 ml of ethanethiol was added. The liquid mixture was cooled and stirred to hold the temperature at 35°C or less, and 30 minutes later 18 ml tetrahydrofuran and 15 ml of 20% hydrochloride were added and heated up to a reflux temperature. After adding 18 ml water and 25 ml saturated saline with stirring, the mixture was cooled down to a room temperature. The resultant precipitate was filtered and washed with 30 ml water, 40 ml of 25% tetrahydrofuran water solution, and 35 ml water, in this order. The resultant solid was dried in vacuum at 40°C to obtain 26 g of crude product of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt (melting point: 217°C).

To a 5L-volume flask were added 200 g of the resultant crude product of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt together with 4400 ml of methanol and 60 ml of deionized water. After the resultant slurry was subjected to the heat reflux, the greater part of crude product was dissolved. The remaining solid was removed in a depressurized condition by use of filtration assist. A distillator was equipped with flask and a solvent was removed until the solution volume was reduced to 1800 ml. After the removal of the mantle heater, the solution was gradually cooled overnight while stirring at a certain speed. A crystalline product was filtered in a depressurized condition and the flask was washed with filtrate to collect a remaining product. The crystal was washed twice with 100 ml cooled methanol (0°C or less) on the filter and subjected to vacuum drying at 60°C to obtain 140 g of product.

This product was formed into a slurry with 3000 ml methanol and 42 ml water and subjected to heat reflux, and then gradually cooled. As aforementioned, the product was filtered and dried to obtain 121g product of high purity (Melting point: 259 to 260°C).

(Powder X-ray diffraction measurement condition)
- Device: Empyrean (manufactured by Spectris Co., Ltd.)
- Target: Cu
- Scanning axis: 2θ-θ
- X-ray output: 40 mA, 45 kV
- Measurement range: 5-40°
- Step size: 0.0260°
- Scanning step time: 197.1150(S)

Period

Evidence A No. 6

Experimental Report

December 14, 2015

Ryoto Fine Co., Ltd.
Technical Department Osamu Okamoto

1. Objectives

To synthesize 6-hydroxy2-(4-hydroxyphenyl)3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt (raloxifene hydrochloride) by implementing the replication study of Examples 18 and 20 described in Japanese Unexamined Patent Application Publication No.57-181081 and characterize its properties.

2. Experiment

The following synthesis experiment and measurement were conducted from November 17, 2014 to December 22, 2014. In addition, the experiment was conducted in the laboratory of Ryoto Fine Co., Ltd (Chiba Prefecture, Kashiwa city, Takada 1410).

A liquid mixture consisting of 17.15 g of 4-(2-pyperidinoethoxy)benzoic acid hydrochloride, 230 ml of chlorobenzene, 34.3 ml of thionyl chloride, and 0.4 ml of dimethylformamide was stirred for 2 hours at 75 to 79°C and its volume was reduced under depressurized condition to a total volume of 130 ml. To the concentrate 230 ml chlorobenzene was added, and then the mixture was subjected to depressurized condensation again to reduce its total volume to 130 ml. To the liquid mixture were added 170 ml of dichloromethane, 15.43 g of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene, 57.15 g of aluminum chloride, and 170 ml of dichloromethane, and then the mixture was stirred for 90 minutes at 27 to 29°C. Thereafter, 18.3 ml of ethanethiol was added and the mixture stirred with cooling for 30 minutes at 35°C or less. After adding 210 ml of tetrahydrofuran and 85 ml of 20% hydrochloride, 210 ml water and 145 ml saturated saline were added and the resultant mixture was stirred. After cooling down to room temperature, the resultant precipitate was filtered and washed with 170 ml water, 230 ml of 25% tetrahydrofuran water solution, and 200 ml water, in this order. The resultant solid was dried in vacuum at 40°C to obtain 27.04 g of crude product of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt.

To 27.00 g of the resultant crude product of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt were added 594 ml of methanol and 8.1 ml of deionized water, and the mixture was subjected to the heat reflux, followed by depressurized filtration. The solvent was removed to leave about 240 ml solution. The solution was gradually cooled overnight while stirring at a certain speed. After depressurized filtration of a crystalline product, the product was washed twice on the filter with 14 ml cooled methanol, and dried in vacuum at 60°C to obtain 15.70 g product.

This product was formed into a slurry with 336 ml methanol and 4.7 ml water and subjected to heat reflux, and then gradually cooled. After filtration and drying, 11.40 g crystal was obtained.

3. Results

Various measurements were implemented for the crystal finally obtained in section 2.

(1) ^{1}H-NMR measurement

Measurement device: BRUKER 250 MHz

Measurement result: Measurement result is shown in Figure 1.

1.6-1.8(6H,m), 2.8-3.1(2H,m), 3.3-3.6(4H,m),
4.4(2H,t), 6.6-7.7(11H,m), 9.8(2H)

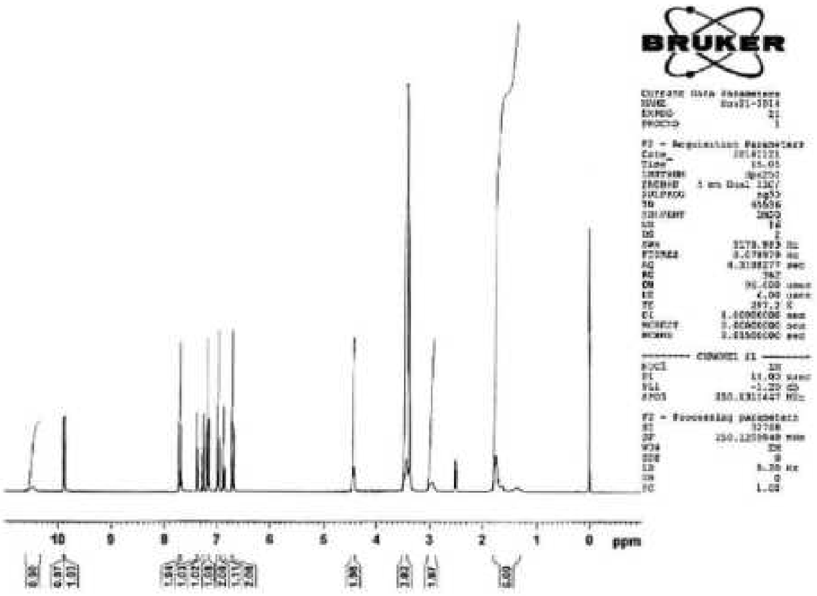


図１　２．で得られた結晶のＮＭＲチャート　Figure 1 NMR chart of crystal obtained in section 2.

(2) Powder X-ray diffraction

Measurement device: Empyrean (manufactured by Spectris Co., Ltd.)

The measurement conditions are set forth below:

- Target: Cu
- Scanning axis: 2θ-θ
- X-ray output: 40 mA, 45 kV
- Measurement range: 5-40°
- Step size: 0.0260°
- Scanning step time: 197.1150(S)

Measurement result: The resultant chart is shown in Figure 2, and the peak search result is shown in Table 1.

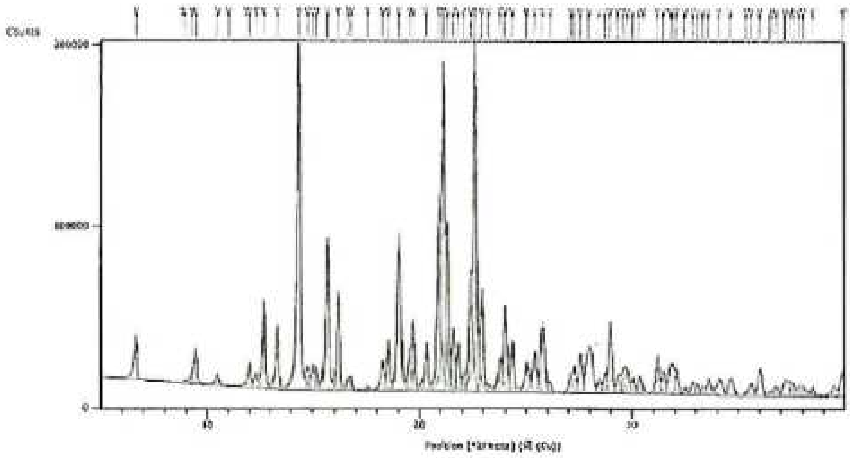
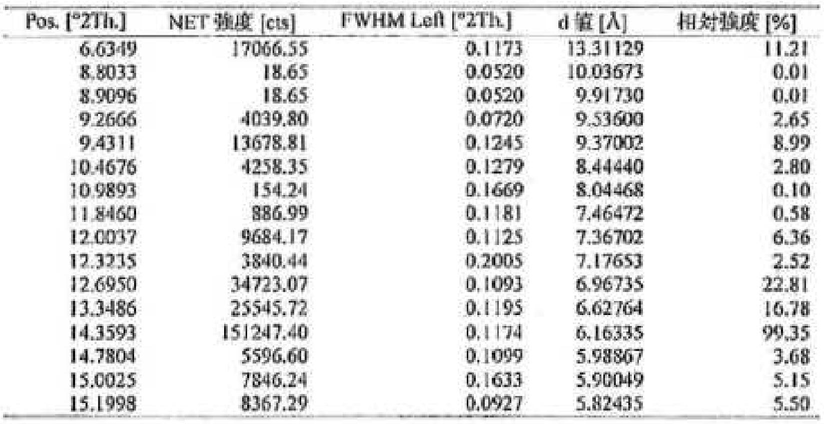


図２．　２．で得られた結晶の粉末Ｘ線回折チャート

図２．　２．で得られた結晶の粉末Ｘ線解析チャート　　Figure 2. A powder X-ray diffractometry chart of crystal obtained in section 2.

表１．図２のピークサーチ結果



Pos. [°2Th.]	NET 強度 [cts]	FWHM Left [°2Th.]	d 値 [Å]	相対強度 [%]
6.6349	17066.55	0.1173	13.31129	11.21
8.8033	18.65	0.0520	10.03673	0.01
8.9096	18.65	0.0520	9.91730	0.01
9.2666	4039.80	0.0720	9.53600	2.65
9.4311	13678.81	0.1245	9.37002	8.99
10.4676	4258.35	0.1279	8.44440	2.80
10.9893	154.24	0.1669	8.04468	0.10
11.8460	886.99	0.1181	7.46472	0.58
12.0037	9684.17	0.1125	7.36702	6.36
12.3235	3840.44	0.2005	7.17653	2.52
12.6950	34723.07	0.1093	6.96735	22.81
13.3486	25545.72	0.1195	6.62764	16.78
14.3593	151247.40	0.1174	6.16335	99.35
14.7804	5596.60	0.1099	5.98867	3.68
15.0025	7846.24	0.1633	5.90049	5.15
15.1998	8367.29	0.0927	5.82435	5.50

表１．図２のピークサーチ結果	Table 1. Peak search result of Figure 2
ＮＥＴ強度［ｃｔｓ］	NET intensity [els]
ｄ値［Å］	d-value [angstrom]
相対強度［%］	Relative Intensity [%]

15.6684	61894.06	0.1187	5.65121	40.66
16.1769	40201.19	0.1200	5.47471	26.41
16.6302	4210.15	0.1653	5.32648	2.77
16.7753	4297.09	0.1151	5.28072	2.82
17.5385	1697.89	0.1060	5.05262	1.12
18.2544	11594.40	0.1458	4.85606	7.62
18.5371	21020.78	0.1130	4.78263	13.81
19.0337	62555.26	0.1746	4.65894	41.09
19.5582	12372.50	0.1913	4.53517	8.13
19.7104	29696.76	0.1048	4.50049	19.51
20.3236	19484.50	0.1281	4.36607	12.80
20.9180	72084.64	0.1690	4.24333	47.35
21.1247	130556.10	0.1293	4.20228	85.76
21.3137	66742.92	0.1079	4.16543	43.84
21.5792	24628.95	0.1349	4.11477	16.18
21.8031	19706.67	0.1209	4.07302	12.95
22.0645	5798.45	0.1488	4.02535	3.81
22.4194	33741.05	0.2196	3.96243	22.16
22.5989	152230.70	0.1209	3.93137	100.00
22.9233	39461.97	0.1578	3.87646	25.92
23.2680	1988.56	0.1259	3.81980	1.31
23.7569	12233.53	0.1924	3.74229	8.04
23.9922	37204.62	0.1279	3.70612	24.44
24.3215	20739.16	0.1475	3.65668	13.62
25.0164	11968.94	0.1458	3.55666	7.86
25.3646	15594.92	0.2095	3.50862	10.24
25.7506	28610.79	0.2045	3.45689	18.79
26.0997	3856.59	0.1516	3.41144	2.53
27.0884	5835.16	0.1851	3.28913	3.83
27.2553	9829.68	0.1459	3.26937	6.46
27.5522	16727.90	0.1456	3.23481	10.99
27.9655	17882.95	0.3202	3.18794	11.75
28.4444	5665.74	0.1835	3.13534	3.72
28.7273	6504.56	0.1877	3.10510	4.27
28.9560	32240.47	0.1365	3.08109	21.18
29.3452	7051.95	0.2017	3.04111	4.63
29.5828	7709.16	0.1430	3.01722	5.06
29.7475	8259.97	0.2126	3.00089	5.43
30.0342	5665.40	0.1621	2.97290	3.72
30.3435	7533.66	0.1524	2.94329	4.95
30.5215	2678.28	0.1152	2.92653	1.76
31.2133	16412.73	0.1555	2.86323	10.78
31.4997	10140.34	0.1372	2.83784	6.66
31.8378	11829.53	0.2340	2.80848	7.77
32.0621	7358.96	0.1474	2.78934	4.83
32.4858	2565.34	0.1290	2.75392	1.69
32.8206	5112.65	0.1627	2.72659	3.36
33.0318	3502.39	0.1336	2.70964	2.30
33.3021	3040.34	0.1409	2.68826	2.00
33.5886	6105.98	0.1807	2.66598	4.01
34.0843	5830.87	0.3025	2.62833	3.83
34.6178	6203.42	0.2336	2.58904	4.08
35.3821	1713.77	0.1128	2.53484	1.13
35.5888	4909.73	0.1830	2.52059	3.23
35.9986	10756.24	0.1936	2.49283	7.07
36.4835	1730.66	0.1801	2.46081	1.14
36.6064	3524.94	0.0758	2.45282	2.32
36.7500	4018.83	0.1303	2.44357	2.64
37.1850	5947.22	0.2585	2.41598	3.91
37.4233	3099.22	0.1602	2.40114	2.04
37.5570	3030.54	0.1616	2.39290	1.99
37.8380	2176.68	0.1433	2.37577	1.43
38.0154	2798.47	0.3245	2.36509	1.84
38.4653	3845.87	0.1278	2.33846	2.53
39.9055	10552.08	0.2564	2.25732	6.93

(3) Drying loss test

Measurement result: 1g of crystal was weighed and dried in an isothermal drier (105°C, 3 hours), but its weight loss was not observed.

(4) Melting point measurement

Measurement device: BUCHI 510 Melting Point

Measurement result: 256 to 261°C

4 Conclusion

The replication study of Examples 18 and 20 described in Japanese Unexamined Patent Application Publication No.57-181081 successfully resulted in a crystal of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyperizinoethoxy)benzoyl]benzo[b]thiophene hydrochloride salt (raloxifene hydrochloride) shown in Figure 2.

Period