Trial decision

Invalidation No. 2016-800111

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The decision on the case of the patent invalidation trial between the above parties on Japanese Patent No. 3224544, entitled" Pharmaceutical Composition containing

Selected Lanthanum carbonate Hydrates," dated August 7, 2017 came with a court decision of revocation of the previous trial decision (2017 (Gyo-Ke) 10171, rendition of decision on September 19, 2018) at the Intellectual Property High Court, the case was proceeded further, and another trial decision was handed down as follows:

Conclusion

The patent for the inventions according to Claims 1 to 8 of Patent No. 3224544 shall be invalidated.

The costs in connection with the trial shall be borne by the Demandee.

Reasons

No. 1 History of the procedures

The application of the inventions for Patent No. 3224544 (hereinafter, referred to as "the Patent") was filed on March 19, 1996 as an international filing date (priority claim under the Paris Convention: March 25, 1995, Great Britain (GB)) and the establishment of patent right was registered on August 24, 2001.

For this, the Demandant requested an invalidation trial for the Patent by the written demand for trial dated September 15, 2016 to invalidate the Patent.

The history of the further procedures is as follows:

dated February 13, 2017 A written answer (the Demandee)

dated March 15, 2017 Notification of matters to be examined (the body)

dated May 25, 2017 Oral proceedings statement brief (the Demandant)

dated May 25, 2017 Oral proceedings statement brief (the Demandee)

June 8, 2017 First oral proceedings

dated June 15, 2017 A written statement (the Demandee)

dated June 22, 2017 A written statement (the Demandant)

dated August 7, 2017 A trial decision

(The demand for trial of the case was groundless.)

September 8, 2017 Access to Intellectual Property High Court

September 19, 2018 A court decision of revocation of the previous trial decision (2017 (Gyo-Ke) 10171, rendition of decision

(Revocation of the trial decision)

dated April 24, 2019 A preliminary notice of trial decision

The Demandee made no response to the preliminary notice of trial decision within the specified period.

No. 2 The Patent Invention

The inventions of Claims 1 to 8 in the Scope of Claims of the Patent are specified by the matters stated in Claims 1 to 8 in the Scope of Claims of the Patent as follows (hereinafter, respectively referred to as "Patent Invention 1" to "Patent Invention 8" and collectively referred to as "the Patent Invention:"

"[Claim 1]

A pharmaceutical composition for the treatment of hyperphosphatemia, comprising lanthanum carbonate of formula $La_2(CO_3)_3 \cdot xH_2O$

where x has a value from 3 to 6, in admixture or association with a pharmaceutically acceptable diluent or carrier.

[Claim 2]

A composition according to Claim 1, wherein in the lanthanum carbonate, x has a value from 3.5 to 5.

[Claim 3]

A composition according to Claim 2, wherein in the lanthanum carbonate, x has a value from 3.8 to 4.5.

[Claim 4]

A composition according to any one of Claims 1 to 3, in a form suitable for oral administration.

[Claim 5]

A composition according to any one of Claims 1 to 4 in unit dosage form to provide from 0.1 to 20g/day.

[Claim 6]

The use of lanthanum carbonate as defined in any one of Claims 1 to 3, for the

preparation of a medicament for the treatment of hyperphosphatemia by administration into the gastrointestinal tract.

[Claim 7]

A process for the preparation of pharmaceutical composition comprising lanthanum carbonate as defined in any one of Claims 1 to 3 which comprises the steps of:

(i) reacting lanthanum oxide with a hydrochloric acid to give lanthanum chloride;

(ii) reacting a solution of the thus obtained lanthanum chloride with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate;

(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of crystallization water; and

(iv) mixing the lanthanum carbonate obtained in step (iii) with a pharmaceutically acceptable diluent or carrier.

[Claim 8]

The use of lanthanum carbonate as defined in any one of Claims 1 to 3, for the preparation of a medicament for the treatment of hyperphosphatemia in a patient with renal failure."

No. 3. Allegations of the parties and means of proof submitted by the parties

3-1 Reasons for invalidation alleged by the Demandant and means of proof submitted by the Demandant

According to the written demand for trial and the oral proceedings statement brief submitted by the Demandant, the Demandant alleged that the inventions of Claims 1 to 8 in the Scope of Claims of Japanese Patent No. 3224544 have the following reasons for invalidation 1 to 3 and submitted the following documentary evidences (each of them is a copy of the original) as means of proof as stated below.

[Reason for invalidation 1] (violation of support requirements)

The statements in the Scope of Claims of the Patent do not comply with the requirement under Article 36(6)(i) of the Patent Act. The Patent for Inventions 1 to 8 falls under Article 123(1)(iv) of the Patent Act and should be invalidated.

[Reason for invalidation 2] (violation of enablement requirement)

The descriptions in the Detailed Description of the Invention of the Patent do not comply with the requirement under Article 36(4) of the Patent Act, of which the provisions then in force shall remain applicable according to revision supplement Article 2(1) of the Act No. 24 of April 17, 2002. Thus, Patent Inventions 1 to 8 should be invalidated under Article 123(1)(iv) of the Patent Act.

[Reason for invalidation 3] (lack of inventive step)

Inventions 1 to 8 would have been easily made by a person skilled in the art, based on inventions disclosed in publications distributed in Japan or abroad before the application of the Patent was filed. Thus, the Appellant should not be granted the Patent for the Patent Inventions 1 to 8 under the provisions of Article 29(2) of the Patent Act. Inventions 1 to 8 should be invalidated under Article 123(1)(ii) of the Patent Act.

[Means of proof]

- Evidence A No. 1:

Japanese Unexamined Patent Application Publication No. 62-145024

- Evidence A No. 2:

James A. Delmez et al., HYPERPHOSPHATEMIA: ITS CONSEQUENCES AND TREATMENT IN PATIENTS WITH CHRONIC RENAL DISEASE, American Journal of Kidney Diseases, 1992, Vol. 19, No. 4, pages 303 to 317

- Evidence A No. 3:

Translation supervised by Kazuyo Shimai, ANATOMY AND PHYSIOLOGY [II] - HUMAN BODY STRUCTURE AND FUNCTION -, Hirokawa Shoten Co., Ltd., published on August 15, 1979, page 381

- Evidence A No. 4:

Fumio Yano et al., PHOSPHATE BINDER MADE OF EGGSHELL CALCIUM EFFECTIVELY REDUCES SERUM PHOSPHATE IN DIALYSIS PATIENTS, IRYO, 1993, Vol. 47, No. 10, pages 810 to 813

- Evidence A No. 5:

Fumiaki Marumoshi, CORRECT KNOWLEDGE OF CHRONIC RENAL FAILURE, Nankodo Co., Ltd., 1st printing published on November 25, 1983, pages 52 to 53

- Evidence A No. 6:

Edited by Masao Ito et al., Igaku-Shoin's Medical Dictionary, Second Edition, Igaku-Shoin, Ltd., published on February 15, 2009, page 952

- Evidence A No. 7:

Translation supervised by Ken Ikeda, PHARMACEUTICAL DOSAGE FORMS, Ishiyaku Publishers, Inc., published on May 14, 1983, page 39

- Evidence A No. 8:

Toshiyuki Oda, STUDIES ON CRYSTAL WATERS OF LANTHANUM CARBONATES, The research bulletin of the Faculty of Education, Oita University, 1975, Vol. 4, No. 5, pages 1 to 5

- Evidence A No 9:

Isao Sugimoto et al., SOLVATES, AMORPHOUS SOLIDS, AND PHARMACEUTICAL FORMULATIONS, Journal of the Society of Powder Technology, 1985, Vol. 22, No. 2, pages 85 to 97

- Evidence A No. 10:

Yoshinobu Nakai, Ed., New Pharmaceutical Science, 1st Ed., Nanzando, Co., Ltd., published on November 25, 1982, pages 102 to 105

- Evidence A No. 11:

Yasuji Suzuki et al., PHYSICOCHEMICAL PROPERTIES AND POLYMORPHISM OF XIBENOLOL HYDROCHLORIDE, Pharmaceutical Research, 1985, Vol. 16, No. 1, pages 85 to 92.

- Evidence A No. 12

Patrick J. Mineely et al., MOLTEN POTASSIUM PYROSULFATE: REACTIONS OF LANTHANUM METAL AND SIX OF ITS COMPOUNDS, Australian Journal of Chemistry, 1987, Vol.40, No. 7, pages 1309 to 1314

- Evidence A No. 13:

Naohisa Yanagihara et al., SYNTHESIS OF LANTHANIDE CARBONATES, JOURNAL OF THE LESS-COMMON METALS, 1991, Vol. 167, No. 2, pages 223 to 232

- Evidence A No. 14:

CHEMICAL ABSTRACTS, 1986, Vol. 104, No. 25, page 770

- Evidence A No. 15:

Chemistry Dictionary Editing Committee, Ed., Chemistry Dictionary 5, Reduced edition, Kyoritsu Publishing Co., Ltd. published on November 15, 1963, page 735

- Evidence A No. 16:

Yoshiyuki Tanaka (Biochemistry Group, Biological Research Department, Sawai Pharmaceutical Co., Ltd.), Lanthanum carbonate-Phosphorus removal test, May 27, 2016

- Evidence A No. 17:

Akinobu Otsuka et al., Ed., Galenical Pharmacy, Second Revised Edition, Nankodo Co., Ltd., April 10, 1992, pages 1 to 3 and 114 to 115.

- Evidence A No. 18:

Sachiyo Yamada et al., CALCIUM CARBONATE AS A PHOSPHATE BINDER IN HEMODIALYSIS PATIENTS: ASSESSMENT OF ITS EFFICACY AND LIMITATION FROM THE NURSING STANDPOINT, Journal of Japanese Society for Dialysis Therapy, 1989, Vol. 22, No. 2, pages 185 to 190

- Evidence A No. 19:

Jeongsoo Shin et al., PLASMA CALCIUM AND PHOSPHORUS CONTROL IN REGULAR HEMODIALYSIS PATIENTS BY USING ORAL CALCIUM CARBONATE, Journal of Japanese Society for Dialysis Therapy, 1988, Vol. 21, No. 3, pages 341 to 348

- Evidence No. 20:

Masafumi Fukagawa et al., EFFECTS OF LOW CALCIUM

CONCENTRATION DIALYSIS FLUID ON CONTROL OF CALCIUM METABOLISM - THE IMPORTANCE OF ADJUVANT THERAPY -, Kidney and Dialysis, 1993, Vol. 34, No. 4, pages 619 to 626

<The above evidences are attached to the written demand for trial>

- Evidence A No. 21:

H. Schneider et al., HIGH-EFFECTIVE ALUMINIUM FREE PHOSPHATE BINDER, IN VITRO AND IN VIVO STUDIES, Proceedings of the European Dialysis and Transplant Association - European Renal Association, 1983, Vol., 20, pages 725 to 730

- Evidence A No. 22:

H. Schneider et al., ALUMINUM-FREE ORAL PHOSPHATE BINDER, Clinical Nephrology, 1985, Vol. 24, Suppl. No. 1, pages S98 to S102

- Evidence A No. 23:

Mitsuo Ogura et al., DEVELOPMENT OF NON-ALUMINUM PHOSPHATE BINDER. HYDROUS CERIUM OXIDE.: -HYDROUS CERIUM OXIDE, Journal of Japanese Society for Dialysis Therapy, 1986, Vol. 19, No. 8, pages 775 to 778

- Evidence A No. 24:

Mudassir S. Sheikh et al., REDUCTION OF DIETARY PHOSPHORUS ABSORPTION BY PHOSPHORUS BINDERS, The Journal of Clinical Investigation, 1989, Vol. 83, No. 1, pp.66 to 73

<The above evidences are attached to the oral proceedings statement brief dated May 25, 2017>

Hereinafter, the above Evidence A Nos. 1 to 24 are referred to as "A1" to "A24."

3-2 Reasons for invalidation alleged by the Demandee and means of proof submitted by the Demandee

According to the written response and the oral proceedings statement brief submitted by the Demandee, the Demandant alleged that the above reasons for

invalidation 1 to 3 do not exist in the Patent and submitted the following documentary evidences (copies) as means of proof.

[Means of proof]

- Evidence B No. 1:

Examination Handbook for Patent and Utility Model in Japan. Annex A: Case examples of "Examination Guidelines for Patent and Utility Model," JPO, September 2015, 1. Cases pertinent to Description Requirements, Case 10

<The above evidence is attached to the written answer for trial>

Hereinafter, the above Evidence B No. 1 is referred to as "B-1."

3-3 Reason for invalidation 3 (lack of inventive step)

Of the above reasons for invalidation alleged by the Demandant, the gist of reason for invalidation 3 (lack of inventive step) is schematically summarized in the following points A to M.

It should be noted that the wordings "hydration water" and "crystallization water" in the following sentences including quotations or descriptions refer to water molecules contained in compound crystals. Similarly, both the wordings ""○ hydrate salt" and "○ hydrate" ("○ is any Arabic number or numerical multiplier) exist. In both cases, the number of water molecules called hydration water or crystallization water is a value corresponding to "○ (the compounds are collectively referred to as "hydrate."

A A1 describes the matters (A) to (G) stated below, so that it discloses an invention including the following constituent components: (the written demand for trial, pages 32 to 34)

a: A phosphate ion-immobilizing agent, comprising

b': lanthanum carbonate monohydrate [$La_2(CO_3)_3 \cdot H_2O$], wherein
c: a sodium carbonate aqueous solution is added to a lanthanum chloride aqueous solution to generate a precipitate, and

the precipitate is filtered, washed with water, and then dried at 100°C, thereby

resulting in
d: the above composition.

(A) "phosphate ion-immobilizing agent" ("Title of the Invention", page 1, left column, line 2)
(B) "A phosphate ion-immobilizing agent consisting of a rare earth element carbonate or organic acid compound." ("Claims," page 1, left column, lines 3 to 5)
(C) "The present invention relates to a novel agent for fixing phosphate ions, particularly those present in a biological fluid." ("Field of Industrial Application," page 1, left column, lines 8 to 10)
(D) "It is well known that in patients with chronic renal failure, hyperphosphatemia is caused by impaired excretion of phosphorus, and dietary restriction and administration of aluminum hydroxide are mainly performed as treatments for this. ... (omitted) ... oral administration of aluminum hydroxide usually requires 1 to 3 g to be taken 3 to 6 times a day, which not only causes discomfort to the patient but also is a causative agent of dialysis encephalopathy and osteoporosis recently. There has been some suspicion that there is concern over the harmful effects of its long-term use.

In response to the above problems, a method using a zirconium compound as an adsorbent has been proposed as a method for removing phosphorus instead of aluminum hydroxide administration ... (omitted) ... . However, the phosphorus adsorption capacity of the zirconium compound is similar to that of aluminum hydroxide, and the amount used cannot be reduced." ("Conventional Art," page 1, left column, line 11 to right column, line 13).
(E) "Since the inorganic ion exchanger adsorbs anion species other than phosphate ions, particularly when applied to a living body, there is a risk of disturbing the ion balance in the body, There are problems that the solubility in acid and alkaline solutions cannot be ignored, and that the amount of adsorption is insufficient and the amount of use increases." ("Problems to be solved by the Invention," page 1, right column, line 14 to page 2, upper left column, line 1)
(F) "As a result of investigating the reactivity of various metal salts with phosphate ions, the present inventors have found that carbonates or organic acid compounds of rare earth elements efficiently interact with phosphate ions. As a result of discovering that they react with each other and conducting extensive studies for practical use, the present invention has been completed.

Therefore, an object of the present invention is to provide an efficient immobilizing agent for phosphate ions, particularly an immobilizing agent effective for

living organisms.

... (Omitted) ...

The immobilizing agent of the present invention selectively and irreversibly reacts with phosphate ions within the pH range in the digestive system of the living body and blood to immobilize the immobilizing agent, and therefore, the immobilization performance of phosphate ions per unit weight is 5 times or more that of the conventional adsorbent method.

Hereinafter, the immobilizing agent of the present invention will be described in detail.

The rare earth element carbonate or organic acid compound of the present invention is a carbonate or organic acid compound of a rare earth element, i.e., Y, La, ... (omitted) ... . Carbonates include simple carbonates or double salts containing alkali metals or alkaline earth metals." ("Means for Solving the Problems," page 2, upper left column, line 2 to upper right column, line 6)

(G) "Example 11

An example of using lanthanum carbonate monohydrate [$La_2(CO_3)_3 \cdot H_2O$] as a phosphate ion-immobilizing agent is shown below.

A sodium carbonate aqueous solution was added to a lanthanum chloride aqueous solution to generate a precipitate. Then, the precipitate was filtered and washed with water, followed by being dried at 100°C.

In a manner similar to that of Example 2, the phosphate ion-immobilizing agent was added to a solution having a phosphate ion concentration of 2.76 mM/l at a rate of 0.6 g/l, and then the phosphate ion extraction coefficient after 2 hours was determined. As a result, the extraction coefficient was 90%." (page 5, upper right column, line 3 to upper right column, line 13)

B Patent Invention 1 and the invention disclosed in the above A1 are identical in that

"A pharmaceutical composition for the treatment of hyperphosphatemia comprising

lanthanum carbonate in admixture or association with a pharmaceutically acceptable diluent or carrier"

and are different in that

"Patent Invention 1 is a pharmaceutical composition comprising lanthanum carbonate (lanthanum carbonate tri- to hexa-hydrate) represented by $La_2(CO_3)_3 \cdot xH_2O$ (x = 3 to 6), whereas Invention A1 is a pharmaceutical composition comprising lanthanum carbonate (lanthanum carbonate monohydrate)." (the written demand for trial, pages

34 to 36)

C Lanthanum carbonate hydrate contains crystallization water (A8), while hydrate was treated as a crystalline polymorph in a broad sense (A9). Thus, it can be said that lanthanum carbonate hydrate was known to be a type of polymorph with crystallization water.

Regarding crystalline polymorph, it is known that "thermodynamically, polymorphs are considered as separate phases, and each polymorph has its own melting point and solubility" (A10), and "it was known that when polymorphisms are present in pharmaceutical products, their crystal forms differ in solubility, hygroscopicity, etc., and as a result, they affect stability and bioavailability." Even before the priority date of the Patent invention, "many studies were conducted on polymorphisms" (A11). It was also known that the phosphorus adsorbing effect differs depending on the crystal structure of the phosphorus adsorbent (A4).

In addition, since the efficient removal of phosphoric acid was an issue in the invention disclosed in Exhibit A1, a person skilled in the art would have a motivation to prepare lanthanum carbonate having a different hydrate.

Therefore, in lanthanum carbonate hydrate with a crystalline polymorph, examining how changing the value of hydrate alters its crystalline to cause a variation in medicinal effect was already common general technical knowledge before the priority date of the Patent Invention, and would be a natural consequence for a person skilled in the art.

Then, lanthanum carbonate trihydrate (A12), pentahydrate (A13), and hexahydrate (A14) were publicly known before the priority date of the Patent, and their manufacturing methods were also extremely easy for a person skilled in the art (A15). Thus, limiting the lanthanum carbonate hydrates to tri- to penta-hydrates is merely to optimize the range of hydrates or make them favorable, and besides, it is a manifestation of the normal creative ability of and merely a design matter for a person skilled in the art, or alternatively, it could be easily conceived by a person skilled in the art by applying common general technical knowledge to Invention A1. (The written demand for trial, pages 36 to 39)

D In addition, from the following experiments conducted by the Demandant and the results (A16), it can be said that the Patent Invention 1 does not have a "remarkable effect" in terms of the ability to remove phosphoric acid, as compared with lanthanum carbonate octahydrate, which was known before the priority date of Invention 1. (The

written demand for trial, pages 39 to 43)

E The specification of the case does not disclose at all the amount of lanthanum carbonate hydrate flowing into the bloodstream, which is out of the scope of the Patent Invention. Then, Patent Invention 1 cannot be said to have a remarkable effect compared to the conventionally known lanthanum carbonate hydrate in terms of the amount thereof flowing into the bloodstream. (The written demand for trial, pages 43 to 45)

F Therefore, a person skilled in the art could have easily made Patent Invention 1 based on the invention disclosed in A1 and the common general technical knowledge. (The written demand for trial, page 46)

G In addition, Patent Inventions 2 and 3 numerically limit x of the lanthanum carbonate of Patent Invention 1 to the range of 3.5 to 5 and 3.8 to 4.5, respectively. However, based on the same grounds as Patent Invention 1, these inventions can be easily prepared from the known tri-, penta-, and hexahydrates of lanthanum carbonate in these numerical ranges, and lack inventive step because of no remarkable effect as use inventions. (The written demand for trial, page 46)

H Furthermore, Patent Invention 4 limits the pharmaceutical composition of any one of Inventions 1 to 3 to a form suitable for oral administration. Examples of the suitable form include tablets, capsules, dragees, suspensions, syrups, and the like as mentioned in the Detailed Description of the Invention of the present specification. However, Evidence A No. 1 describes that "The phosphate ion-immobilizing agent of the present invention ... can be used in the form of being encapsulated with a polysaccharide ... or the like." and, moreover, the above suitable form was common general technical knowledge as pharmaceutical compositions (A17 and A7). Therefore, Patent Invention 4 lacks an inventive step. (The written demand for trial, page 46)

I Furthermore, Patent Invention 5 limits the pharmaceutical composition of any one of Claims 1 to 4 in unit dosage form to provide from 0.1 to 20g/day. However, the dose was commonly used at the time of the priority date and nothing more than a matter of common general technical knowledge (A4, A18, A19, and A20). Thus, Patent Invention 5 lacks an inventive step. (The written demand for trial, pages 46 to 47)

J Patent Invention 6 limits the use of the pharmaceutical composition of any one of Claims 1 to 3 to administration into the gastrointestinal tract. However, A1 describes that "It is considered that the phosphate ion immobilization ... of the rare earth element of the present invention proceeds efficiently in the digestive system beyond the stomach." Thus, Patent Invention 6 lacks an inventive step. (The written demand for trial, page 47)

K Patent Invention 7 defines a process for the preparation of the pharmaceutical composition of any of Inventions 1 to 3. However, A1 discloses an example in which a lanthanum chloride aqueous solution is solidified by addition of a sodium carbonate aqueous solution and drying. Also, A15 describes that "Process for preparation: Alkali metal carbonate is added to an aqueous solution of lanthanum salt, and the resulting precipitate is dried at 100°C to obtain monohydrate or dried at room temperature to obtain octahydrate. Passing carbon dioxide through a suspension of hydroxide gives a trihydrate." Thus, the process for preparation in Patent Invention 7 is just a common process for preparation. Therefore, Patent Invention 7 lacks an inventive step. (The written demand for trial, page 47)

L Patent Invention 8 limits the use of the pharmaceutical composition of any one of Inventions 1 to 3 to the treatment of hyperphosphatemia in a patient with renal failure. However, A1 describes that "It is well known that in patients with chronic renal failure, hyperphosphatemia is caused by impaired excretion of phosphorus." Thus, Patent Invention 8 lacks an inventive step. (The written demand for trial, pages 47 to 48)

M Consequently, a person skilled in the art could have easily made the Patent Invention based on the invention and the common general technical knowledge described in A1 or the technical matters described in A15, and thus it falls under Article 29(2) of the Patent Act. Therefore, the Patent should be invalidated pursuant to the provisions of Article 123(1)(ii) of the Patent Act.

No. 4 Judgment by the body

The body determines that the patent for Patent Inventions 1 to 8 should be invalidated by the Reasons for invalidation 3. The reasons are follows:

4-1 Fact-finding and legal decision-making necessary for deriving the main sentence of the court decision on the revocation of the previous trial decision (2017 (Gyo-Ke) 10171) and the binding effect thereof on the body

"When a decision to revoke the trial decision is finalized in a suit against trial decision for the patent invalidation trial, the trial examiner shall carry out further proceedings on the case of the trial in accordance with the provisions of Article 181(2) of the Patent Act to make a trial decision. However, a suit against the trial decision is subjected to the Administrative Litigation Act. Thus, the re-trial or trial decision is subject to the binding effects of the decision to revoke the trial decision pursuant to the provisions of Article 33(1) of the same Act. The binding effects extend to the fact-finding and legal decision-making necessary for deriving the main sentence of the court decision. Thus, the trial examiner is not allowed to make a finding that conflicts with the finding in the revocation decision." (the judgment of the Third Petty Bench of the Supreme Court, April 28, 1992 (1988 (Gyo-Tsu), 10, Minshu, Vol. 46, No. 4, page 245). The court decision on the revocation of the previous trial decision indicates the following recognition judgments: (Judgment 1) to (Judgment 5). It is recognized that all of these judgments are necessary for the main text of the above decision to be derived. Thus, the recognition judgments bind the body.

4-2 Recognition judgments in the court decision on the revocation of the previous trial decision

(In the text, the numbers described as ▲1▼, etc. are circled numbers in the original text.)

(Judgment 1)
"(3) Regarding the common general technical knowledge and well-known art at the time of the priority date of the present application

... (Omitted) ...

B Common general technical knowledge or well-known art related to medicaments existing as hydrates

In summary of the described matters in the above A, at the time of the priority date of the present application (March 25, 1995), since ▲1▼ lanthanum carbonate hydrates with different numbers of hydration water molecules can be obtained by adjusting the drying conditions, such as drying temperature; and ▲2▼ in a medicament that exists as a hydrate, differences in the number of water molecules (hydration water)

can affect the solubility, dissolution rate, and bioavailability of a medicinal substance and the chemical and physical stability of the medicament, it is common general technical knowledge or a well-known art to, during the development of the drug, investigate whether a compound under consideration forms a hydrate and, if the presence of a hydrate is confirmed, compare the compound with an anhydride or another hydrate of the same compound having a different numbers of hydration water molecules to prepare the optimum one." (The written court decision, page 35, line 2 from the bottom to page 40, line 14)

(Judgment 2)

"(4) Existence of easily-conceived property of Different Feature 1

A As an invention of "an efficient immobilizing agent for phosphate ions, particularly an immobilizing agent effective for living organisms" for the treatment of hyperphosphatemia caused by impaired phosphorus excretion in patients with chronic renal failure, A1 discloses "a phosphate ion-immobilizing agent consisting of a rare earth element carbonate or an organic acid compound." As stated in the above ... , a lanthanum carbonate monohydrate salt (monohydrate) disclosed as one of the examples (Example 11) had a phosphate ion extraction coefficient of 90%.

In light of the common general technical knowledge or well-known art at the time of the priority date of the present application recognized in the above (3)B, with respect to the lanthanum carbonate monohydrate (Invention A1) disclosed in A1, it is recognized that a person skilled in the art in contact with A1 could have been motivated to prepare lanthanum carbonate hydrates with different numbers of hydration water molecules in search of a phosphate ion-immobilizing agent with a higher phosphate ion extraction coefficient as well as excellent solubility, dissolution rate, chemical stability, and physical stability.

It is recognized that a person skilled in the art could easily conceive of adjustment of drying conditions, such as the drying temperature, to make the configuration of the lanthanum carbonate monohydrate (Invention A1) disclosed in A1 into the configuration of the lanthanum carbonate hydrate with the number of hydration water molecules in the range of 3 to 6 (corresponding to the configuration of Invention 1 relating to Different Feature 1).

The judgment of this trial decision, which is different from this, is incorrect because it does not take into account the common general technical knowledge or well-known art at the time of the priority date of the present application certified in the above (3)A. (The written court decision, page 40, line 15 to page 41, line 6)

(Judgment 3)

"(5) Presence or absence of remarkable effect of Invention 1

A ... (Omitted) ...

(A) On the promise that a person skilled in the art could easily conceive of making the lanthanum carbonate monohydrate (Invention A1) disclosed in A1 into the configuration of Invention 1 relating to Different Feature 1 in which the number of hydration water molecules is in the range of 3 to 6 (the above (4)A), whether Invention 1 has a remarkable effect that could not be predicted by a person skilled in the art due to the configuration of Invention 1 relating to Different Feature 1 should be judged from the viewpoint of whether the effect of Invention 1 is different from the effect that could be predicted from the technical level at the time of the priority date of the present application when a person skilled in the art in contact with A1 made the lanthanum carbonate monohydrate (Invention A1) disclosed in A1 into the configuration of Invention 1 relating to Different Feature 1, or, even if it is the same quality, whether it is far superior to the prediction of a person skilled in the art.

(B) For consideration, the present specification describes that, as the results of carrying out tests in which samples of lanthanum carbonate hydrate with different numbers of hydration water molecules were added to stock solutions each containing phosphate adjusted to pH 3 and then the phosphate binding capabilities (the percentages of phosphate removed) of the samples were measured at time intervals of 0.5 to 10 minutes, as shown in Table 1 (Attachment 1), the percentage of phosphate removed at 5 minutes was 70.5% for $La_2(CO_3)_3 \cdot 8.8H_2O$ ("Sample 1"), 39.9% for $La_2(CO_3)_3 \cdot 1.3H_2O$ ("Sample 2"), 96.5% for $La_2(CO_3)_3 \cdot 4.4\ H_2O$ ("Sample 3"), 76.3% for 1 $La_2(CO_3)_3 \cdot 2.2H_2O$ ("Sample 4"), and 100% for lanthanum carbonate tetrahydrate $4H_2O$ ("Sample 5") and $La_2(CO_3)_3 \cdot 3.8H_2O$ ("Sample 6"). This description represents that the percentage of phosphate removed at 5 minutes is 96.5% or 100% for $La_2(CO_3)_3 \cdot 4.4H_2O$ ("sample 3"), $La_2(CO_3)_3 \cdot 4H_2O$ ("sample 5"), and $La_2(CO_3)_3 \cdot 3.8\ H_2O$ ("sample 6"), which is higher than the percentage of phosphate removed for other lanthanum carbonate hydrates ("samples 1, 2, and 4") out of the scope of Invention 1.

On the other hand, A1 describes that a phosphate ion extraction coefficient of 90% was as a result of an experiment ("a phosphate ion extraction experiment") in "Example 11" in which lanthanum carbonate monohydrate [$La_2(CO_3)_3 \cdot H_2O$] was added to a solution having a phosphate ion concentration of 2.76 mM/l at a ratio of 0.6 g/l, and stirred at room temperature for 2 hours while being retained at pH7 by addition of a 1N sodium hydroxide aqueous solution. This description indicates that the phosphate ion

extraction coefficient of lanthanum carbonate monohydrate of Invention A1 is 90% at 2 hours after stirring in an aqueous solution adjusted to pH 7.

First, according to the above findings, it can be said that the test results described in the present specification and the experimental results described in A1 show the same quality effect of "percentage of phosphate removed" or "phosphate ion extraction coefficient" of lanthanum carbonate hydrate.

Next, the experimental conditions differ between the test described in the present specification and the experiment described in A1 in terms of the pH value of the aqueous solution, the time of measurement of the extraction coefficient, and the number of measurements. However, for a person skilled in the art who comes into contact with A1, it can be said that measuring the "phosphate ion extraction coefficient" using the same aqueous solution of pH 3 as in gastric juice and also measuring the extraction coefficient at regular intervals would be matters within the range of a design decision that can be done as appropriate in light of the description of A1 that "Since the pH of the body fluid in the living body, particularly in the digestive system, is in the range of about pH 3 in the acidic gastric juice to about pH 8 in the intestinal fluid which is weakly alkaline, the carbonate or organic acid compounds of the rare earth element of the present invention is used. The phosphate ion immobilization of the carbonate or organic acid compounds is considered to proceed efficiently in the digestive system beyond the stomach." and ... .

In addition, for a person skilled in the art, when the lanthanum carbonate monohydrate described in A1 (Invention A1) is configured to the lanthanum carbonate hydrate with the numbers of hydration water molecules in the range of 3 to 6 (corresponding to the configuration of Invention 1 relating to Different Feature 1), it may exceed the percentage of phosphate removed (90%) of the lanthanum carbonate monohydrate and may be within the range that can be predicted to be closer to 100%. Therefore, the effect of the present invention 1 that the percentage of phosphate removed at 5 minutes in an aqueous solution of pH 3 is 96.5% or 100% cannot be recognized to be far superior to the prediction of a person skilled in the art.

Therefore, it cannot be recognized that Invention 1 has a remarkable effect that could not be expected by a person skilled by having a configuration relating to Different Feature 1. Thus, the judgment of the trial decision that admits it is in error." (Written court decision, page 43, line 10 to page 46, line 2)

(Judgment 4)
"(6) Summary

A As stated above, a person skilled in the art could easily conceive of Different Feature 1. However, it cannot be recognized that Invention 1 has a remarkable effect by having a configuration relating to Different Feature 1.

Therefore, without pausing to consider Different Feature 2, the judgment of the trial decision that Invention 1 could not be easily invented by a person skilled in the art based on A1 and common general technical knowledge is incorrect ... ." (Written court decision, page 47, lines 20 to 26)

(Judgment 5)

"2 Ground for revocation 1-2 (error in judgment of inventive step of Inventions 2 to 8)

The trial decision judged that Inventions 2 to 5 depend from Invention 1 to limit the content thereof, Invention 7 is a process for the preparation of Inventions 1 to 3, and Inventions 6 and 8 are the use of lanthanum carbonate used in Inventions 1 to 3 for the preparation of a medicament for the treatment of hyperphosphatemia, and thus, as with Invention 1, Inventions 2 to 8 could not be easily invented by a person skilled in the art based on Invention A1.

However, as stated in the above 1(6)A, given the judgment of the easily-conceived property of Invention 1 made by the trial decision is wrong, the above judgment of the trial decision that denied the easily-conceived property of Inventions 2 to 8 is lacks its premise and is wrong.

Therefore, the Plaintiff's claim for ground for revocation 1-2 is grounded." (The written court decision, page 48, lines 11 to 21)

4-3 Judgment of the body on reason for invalidation 3

On the premise of the above "4-2," the body determines that the Patent should be invalidated by the Reason for invalidation 3 (lack of inventive step) alleged by the Demandant. The reasons are as follows:

4-3-1 Described matters in major evidences

- A1: Japanese Unexamined Patent Application Publication No. 62-145024

In the descriptions picked up from A1, the Chinese character "濾" is represented by adding the radical of "さんずい(sanzui)" to the left side of Chinese character "戸."

(A1-1)

"1 Title of the Invention
Phosphate ion-immobilizing agent" (page 1, left column, lines 2 to 3)

(A1-2)
"2 The scope of claims
A phosphate ion-immobilizing agent consisting of a rare earth element carbonate or organic acid compound." (page 1, left column, lines 4 to 5)

(A1-3)
"The present invention relates to a novel agent for fixing phosphate ions, particularly those present in a biological fluid." (page 1, left column, lines 9 to 10)

(A1-4)
"It is well known that in patients with chronic renal failure, hyperphosphatemia is caused by impaired excretion of phosphorus, and dietary restriction and administration of aluminum hydroxide are mainly performed as treatments for this. ... (omitted) ... In addition, oral administration of aluminum hydroxide usually requires 1 to 3 g to be taken 3 to 6 times a day, which not only causes discomfort to the patient but also is a causative agent of dialysis encephalopathy and osteoporosis recently. There has been some suspicion that there is concern over the harmful effects of its long-term use.

In response to the above problems, a method using a zirconium compound as an adsorbent has been proposed as a method for removing phosphorus instead of aluminum hydroxide administration (Nobuo Nakabayashi, et al .: Treatment of hyperphosphatemia with zirconium, JINKOUZOUKI (Artificial Organs) Vol. 11, 1, pages 36 to 39 (1982), and Japanese Unexamined Patent Application Publication No. 59-46964). However, the phosphorus adsorption capacity of the zirconium compound is similar to that of aluminum hydroxide, and the amount used cannot be reduced. (page 1, left column, line 12 to right column, line 13)

(A1-5)
"Since the inorganic ion exchanger adsorbs anion species other than phosphate ions, particularly when applied to a living body, there is a risk of disturbing the ion balance in the body, There are problems that the solubility in acid and alkaline solutions cannot be ignored, and that the amount of adsorption is insufficient and the amount of use increases." (page 1, right column, line 15 to page 2, upper left column,

line 1)

(A1-6)

"As a result of investigating the reactivity of various metal salts with phosphate ions, the present inventors have found that carbonates or organic acid compounds of rare earth elements efficiently interact with phosphate ions. As a result of discovering that they react with each other and conducting extensive studies for practical use, the present invention has been completed.

Therefore, an object of the present invention is to provide an efficient immobilizing agent for phosphate ions, particularly an immobilizing agent effective for living organisms.

That is, the immobilizing agent of the present invention is a phosphate ion immobilizing agent characterized by comprising a carbonate of a rare earth element or an organic acid compound.

The immobilizing agent of the present invention selectively and irreversibly reacts with phosphate ions within the pH range in the digestive system of the living body and blood to immobilize the immobilizing agent, and therefore, the immobilization performance of phosphate ions per unit weight is 5 times or more that of the conventional adsorbent method." (page 2, left upper column, lines 3 to 19)

(A1-7)

"The rare earth element carbonate or organic acid compound of the present invention is a carbonate or organic acid compound of a rare earth element; i.e., Y, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, or Lu. The carbonates include simple carbonates or double salts containing alkali metals or alkaline earth metals." (page 2, upper right column, lines 1 to 6)

(A1-8)

"The phosphate ion-immobilizing agent of the present invention is an aqueous suspension of a cake obtained by passing the carbonate or organic acid compound of the rare earth element by the above-mentioned preparation method or the like, and a powder obtained by drying the cake, and the powder can be used in the form of being encapsulated with a polysaccharide such as gelatin or carrageenan." (page 2, lower left column, line 18 to lower right column, line 3)

(A1-9)

"The reaction in which the carbonate or organic acid compound of the rare earth element of the present invention fixes phosphate ion can be represented by the following formula.

$Ln_2X_3 \cdot nH_2O + 2MH_2PO_4$

$<=> 2LnPO_4 + 2H_2X + M_2X$

Here, Ln is a trivalent rare earth element, X is a carbonate ion or an organic acid ion (shown as a divalent ion), and M represents an alkali metal or hydrogen ion.

The phosphate ion immobilization of the rare earth element carbonate or organic acid compound according to the above reaction formula is affected by the pH of the liquid phase. For example, the dependence of the phosphate ion extraction coefficient on the liquid phase pH when using cerium oxalate is shown in the drawing. That is, in the strongly acidic region of pH 5 or less, the equilibrium tilts to the left, but in the neutral to alkaline region of pH 6 or above, the equilibrium shifts to the right almost 100%, which makes it possible to perform irreversible phosphate ion immobilization.

Since the pH of the body fluid in the living body, particularly in the digestive system, is in the range of about pH 3 in the acidic gastric juice to about pH 8 in the intestinal fluid which is weakly alkaline, the phosphate ion immobilization of the rare earth element carbonate or organic acid compound is considered to proceed efficiently in the digestive system beyond the stomach.

Further, regarding the immobilization of the phosphate ion of the rare earth element carbonate or the organic acid compound of the present invention, even if other anions, for example, a large amount of ions such as chlorine ions and bicarbonate ions are present in the biological fluid, the phosphate ions can be selectively immobilized.

The rare earth element carbonate or organic acid compound of the present invention immobilizes a phosphate ion as a phosphate of a rare earth element, but the phosphate is insoluble in body fluid and is directly discharged out of the body. (In the original text, "<=>" is represented such that "→" is placed under "←.") (page 2, under right column, line 4 to page 3, upper left column, line 18)

(A1-10)

"Regarding the amount of the phosphate ion-immobilizing agent used in the present invention, in the case of the cerium oxalate decahydrate of the present invention, almost 100% of phosphate ions can be immobilized and removed with 0.17 to 0.51 g with respect to the concentration of phosphate ion present in the biological fluid, for example, at a concentration of 0.46 to 1.36 mM/l of the intestinal juice (see Biochemical Data Book I, The Japanese Biochemical Society, published in 1979). Conventional

aluminum hydroxide gel and zirconium hydroxide containing hydroxide cannot remove 100% of phosphate ions even when the amount used is 10 g. It can be seen that the rare earth carbonate or organic acid compound of the present invention has extremely excellent phosphate ion immobilization performance.

The phosphate ion-immobilizing agent of the present invention, for example, cerium oxalate decahydrate, is a drug described in Pharmacopeia and used as a powder for gastrointestinal catarrh and vomiting of mothers due to its sedative effect. Incidentally, the cerium oxalate is described as a mixture of cerium, neodymium, praseodymium, lanthanum, and oxalates of other homologous elements. A method of taking cerium oxalate decahydrate to remove phosphate ions in biological fluid requires less than the currently used dose of 3 to 6 g/day of aluminum hydroxide, and, at about 1 g/day, exerts a sufficient effect." (page 3, upper left column, line 2 from the bottom to lower left column, line 3).

(A1-11)

"Example 1

The pH dependency of the capability of eliminating phosphate ion-immobilization of the ceric oxalate of the present invention is shown.

Preparation of cerium oxalate decahydrate

After dissolving 99.9% of commercially available cerium chloride in distilled water, a white crystalline precipitate was obtained by addition of an aqueous oxalic acid solution. The crystals were filtered and then washed with water until no chloride ions were found in the filtrate, followed by being air dried in air.

Experiment of eliminating phosphate ion-immobilization

Phosphate ion-containing water was prepared by diluting phosphoric acid (85.6 ppm as phosphorus) with distilled water so as to make a phosphate ion concentration of 2.76 mM/l. Then, cerium decahydrate was added to the aqueous solution at a ratio of 1 g/l. The aqueous solution was stirred at room temperature for 2 hours while being retained at a predetermined pH value by addition of a 1N sodium hydroxide aqueous solution. Subsequently, the mixed solution was filtered, the pH of the filtrate was measured with a pH meter, and the phosphate ion concentration was measured by ion chromatography (device manufactured by Dionex Corporation, type 2020i). The results are shown in the drawing as the relationship between the pH of the solution and the extraction coefficient of phosphate ions.

The precipitate formed at pH 7 was filtered, dried, and then subjected to X-ray diffraction measurement, thereby being found to be cerium monophosphate. In

addition, it was found that 4.1 mM oxalate ion was present in the filtrate and allows the reaction of the following formula to proceed quantitatively.

$Ce_2(C_2O_4)_3 \cdot 10H_2O + 2NaH_2PO_4 \rightarrow$

$2CePO_4 + Na_2C_2O_4 + 2H_2C_2O_4 + (10H_2O)$

Examples 2 to 4

Cerium oxalate decahydrate prepared in a manner similar to that of Example 1 was added to an aqueous solution having a phosphate ion concentration of 2.76 mM/l at a rate of 0.2 g/l, 0.5 g/g, and 1.5 g/l, and stirred at room temperature for 2 hours while being retained at pH7 by addition of a 1N sodium hydroxide aqueous solution. The phosphate ion concentration in the solution was measured in a manner similar to that of Example 1, and the phosphate ion extraction coefficient was measured.

表 1

	固定化剤添加量 (g/l)	セリウムモル数(mM)	リン酸イオン除去率 (%)
実施例 2	0.2	0.55	19
〃 3	0.5	1.38	48
〃 1	1.0	2.76	99
〃 4	1.5	4.14	100

"

表 1　Table 1

実施例　Example

固定化剤添加量　Amount of fixative added

セリウムモル数　Number of cerium moles

リン酸イオン除去率　Phosphate extraction coefficient

(page 3, lower right column, line 3 to page 4, upper right column, line 1, and Table 1)

(A1-12)

"Example 5

The cerium oxalate decahydrate prepared in a manner similar to that of Example 1 was added to an aqueous solution having a phosphate ion concentration of 2.76 mM/l , a chloride ion concentration of 85 mM/l, and a bicarbonate ion concentration of 48 mM/l at a ratio of 1 g/l, and stirred at room temperature for 2 hours while being retained at pH7. As a result, the phosphate ion extraction coefficient was 97%.

Example 6

An example of using cerium carbonate nonahydrate [$Ce_2(CO_3)_3 \cdot 9H_2O$] as a phosphate ion-immobilizing agent is shown below.

After dissolving cerium sulfate (99%, reagent) in distilled water, the resulting aqueous solution was added with an aqueous ammonium carbonate solution to generate a precipitate. Then, the precipitate was washed by decantation with boiling water, air-dried on filter paper, and then dried in a desiccator containing silica gel.

In a manner similar to that of Example 2, the phosphate ion-immobilizing agent was added to a solution having a phosphate ion concentration of 2.76 mM/l at a rate of 0.5 g/l, and then the phosphate ion extraction coefficient after 2 hours was determined. As a result, the phosphate ion extraction coefficient was 98%.

Example 7

An example of using sodium cerium carbonate hexahydrate [$NaCe(CO_3)_2 \cdot 6H_2O$] as a phosphate ion-immobilizing agent is shown below.

A concentrated aqueous solution of primary cerium nitrate was added to a saturated aqueous solution of sodium carbonate to generate a precipitate. The precipitate was filtered, washed with an aqueous solution containing sodium carbonate, and then air-dried at room temperature.

In a manner similar to that of Example 2, the phosphate ion-immobilizing agent was added to a solution having a phosphate ion concentration of 2.76 mM/l at a rate of 1 g/l, and then the phosphate ion extraction coefficient after 2 hours was determined. As a result, the phosphate ion extraction coefficient was 93%.

Example 8

An example of using cerium citrate 3.5-hydrate {$Ce[C_3H_4OH(CO_2)_3] \cdot 3.5H_2O$} as a phosphate ion-immobilizing agent is shown below.

A cerium sulfate aqueous solution was gradually added to a sodium citrate aqueous solution to generate a precipitate. The precipitate was aged until it became crystalline, and then filtered, washed with water, and dried in the air.

In a manner similar to that of Example 2, the phosphate ion-immobilizing agent was added to a solution having a phosphate ion concentration of 2.76 mM/l at a rate of 0.5 g/l, and then the phosphate ion extraction coefficient after 2 hours was determined. As a result, the phosphate ion extraction coefficient was 92%.

Example 9

An example of using cerium malonate hexahydrate [$Ce_2(CH_2C_2O_4)_3 \cdot 6H_2O$] as a phosphate ion-immobilizing agent is shown below.

It was obtained as crystals by adding a potassium malate aqueous solution to a cerium nitrate aqueous solution to generate a precipitate, followed by heating. The crystals were filtered, washed with water, and then dried in air.

In a manner similar to that of Example 2, the phosphate ion-immobilizing agent was added to a solution having a phosphate ion concentration of 2.76 mM/l at a rate of 1 g/l, and then the phosphate ion extraction coefficient after 2 hours was determined. As a result, the phosphate ion extraction coefficient was 100%.

Example 10

An example of using yttrium carbonate [$Y_2(CO_3)_3 \cdot 3H_2O$] as a phosphate ion-immobilizing agent is shown below.

An excess amount of a sodium carbonate aqueous solution was added to an yttrium chloride aqueous solution to generate a precipitate. The precipitate was filtered, washed with water, and then dried in the air.

In a manner similar to that of Example 2, the phosphate ion-immobilizing agent was added to a solution having a phosphate ion concentration of 2.76 mM/l at a rate of 0.5 g/l, and then the phosphate ion extraction coefficient after 2 hours was determined. As a result, the phosphate ion extraction coefficient was 85%." (page 4, upper right column, line 1 under the table to page 5, upper right column, line 2)

(A1-13)

"Example 11

An example of using lanthanum carbonate monohydrate [$La_2(CO_3)_3 \cdot H_2O$] as a phosphate ion-immobilizing agent is shown below.

A sodium carbonate aqueous solution was added to a lanthanum chloride aqueous solution to generate a precipitate. Then, the precipitate was filtered and washed with water, followed by being dried at 100°C.

In a manner similar to that of Example 2, the phosphate ion-immobilizing agent was added to a solution having a phosphate ion concentration of 2.76 mM/l at a rate of 0.6 g/l, and then the phosphate ion extraction coefficient after 2 hours was determined.

As a result, the phosphate ion extraction coefficient was 90%." (page 5, upper right column, lines 3 to 13)

(A1-14)

"Example 12

An example of using neodymium oxalate decahydrate [$Nd_2(C_2O_4)_3 \cdot 10H_2O$] as a phosphate ion-immobilizing agent is shown below.

An oxalic acid aqueous solution was added to a neodymium chloride aqueous solution to generate a precipitate. The precipitate was filtered, washed with water, and then dried in the air.

In a manner similar to that of Example 2, the phosphate ion-immobilizing agent was added to a solution having a phosphate ion concentration of 2.76 mM/l at a rate of 1 g/l, and then the phosphate ion extraction coefficient after 2 hours was determined. As a result, the phosphate ion extraction coefficient was 97%.

Example 13

An example of using gadolinium oxalate decahydrate [$Gd_2(C_2O_4)_3 \cdot 10H_2O$] as a phosphate ion-immobilizing agent is shown below.

An oxalic acid aqueous solution was added to a neodymium chloride aqueous solution to generate a precipitate. The precipitate was filtered, washed with water, and then dried in the air.

In a manner similar to that of Example 2, the phosphate ion-immobilizing agent was added to a solution having a phosphate ion concentration of 2.76 mM/l at a rate of 1 g/l, and then the phosphate ion extraction coefficient after 2 hours was determined. As a result, the phosphate ion extraction coefficient was 92%.

Example 14

An example of using samarium oxalate decahydrate [$Sm_2(C_2O_4)_3 \cdot 10H_2O$] as a phosphate ion-immobilizing agent is shown below.

An oxalic acid aqueous solution was added to a samarium chloride aqueous solution to generate a precipitate. The precipitate was filtered, washed with water, and then dried in the air.

In a manner similar to that of Example 2, the phosphate ion-immobilizing agent was added to a solution having a phosphate ion concentration of 2.76 mM/l at a rate of 1 g/l, and then the phosphate ion extraction coefficient after 2 hours was determined. As a result, the phosphate ion extraction coefficient was 91%." (page 5, upper right column, line 14 to lower right column, line 9)

- A4: Fumio Yano et al., PHOSPHATE BINDER MADE OF EGGSHELL CALCIUM EFFECTIVELY REDUCES SERUM PHOSPHATE IN DIALYSIS PATIENTS, IRYO, 1993, Vol. 47, No. 10, pages 810 to 813

(A4-1)

"Another way to deal with hyperphosphatemia is to use a phosphate binder. Taking the phosphate binder immediately after eating allows P contained in the meal and the adsorbent to react with each other to form an insoluble compound. Therefore, P is less likely to be absorbed from the intestinal tract. In other words, the use of phosphate binder can further reduce the intake of P." (page 811, left column, lines 15 to 20)

(A4-2)

"Case 1: Calcium carbonate = 3.0 g/day
Egg-shell calcium = 12 tablets/day
Case 2: Calcium carbonate = 6.0 g/day
Egg-shell calcium = 24 tablets/day
Case 3: Calcium carbonate = 4.0 g/day
Egg-shell calcium = 16 tablets/day (page 811, right column, lines 22 to 27)

(A4-3)

"Conventionally, aluminum gel has been used as a phosphate binder. --- (Omitted) --- Instead, calcium carbonate is mainly used in Japan." (page 811, left column, lines 21 to 25)

(A4-4)

" Although the main component of egg-cell calcium is the same compound as the Japanese Pharmacopoeia calcium carbonate, a large difference was actually observed in the phosphate-binding effect between the two.

For investigating the mechanism of the difference in phosphate-binding action between the two, we focused on their crystal structures and attempted to make a comparison using a scanning electron microscope.

As shown in Fig. 2, a large difference was observed in the crystal particle structure between the Japanese Pharmacopoeia calcium carbonate and egg-shell calcium, suggesting that the difference between their crystal structures might cause a difference in phosphate-binding effect. That is, the reason may be that the crystals of egg-shell calcium have a large surface area and thus form a large amount of insoluble calcium

phosphate having excellent solubility and ease of binding to phosphate; egg-shell calcium can bind more phosphates when binding phosphate on its surface while maintaining its crystal structure (physical binding); or the like." (page 812, right column, line 33 to page 813, left column, line 5)

- A5: Fumiaki Marushige, Correct knowledge of chronic renal failure, Nankodo Co., Ltd., 1st printing published on November 25, 1983, pages 52 to 53

(A5-1)
"There is an approach taken to prevent phosphorus from being absorbed in the body. Specifically, it is to drink an aluminum preparation such as aluminum gel. Drinking the aluminum preparation causes aluminum to bind to phosphorus contained in food to prevent it from being absorbed through the intestines, thereby raising the blood phosphorus concentration." (page 52, lines 28 to 32)

(A5-2)
"

アルミニウム製剤は腸壁からリンが吸収されないように働く。

An aluminum preparation works to prevent phosphorus from being absorbed through the intestinal wall.

アルミゲル　　Alumigel

"

(page 53)

- A6: Igaku-Shoin's Medical Dictionary, Second Edition, Igaku-Shoin, Ltd., published on February 15, 2009, page 952

(A6-1)

"Hyperphosphatemia ... (Omitted) ... [Hyperphosphatemia, phosphatemia ... (Omitted) ...] means a serum phosphorus level of 4.5 mg/dL or higher. ... (Omitted) ... Hyperphosphatemia = hyperphosphatemia "

- A7: Pharmaceutical dosage forms, Ishiyaku Publishers, Inc., published on May 14, 1983

(A7-1)

" A drug is rarely administered alone but rather is administered as an ingredient in a mixture or combination with a variety of substances other than drugs, by which the drug is pharmaceutically characterized. These substances are not drugs but important to be selected as pharmaceutical additives to make various types of formulations. The roles of the pharmaceutical additives include solubilizing, dispersing, thickening, dilution, emulsifying, stabilizing, preserving, coloring, aromatizing, etc., as well as shaping the drug suitable as a drug without impairing its effectiveness." (page 39, left column, lines 1 to 9)

- A8: Toshiyuki ODA, Studies on Crystal Waters of Lanthanum carbonates, The research bulletin of the Faculty of Education, Oita University, 1975, Vol. 4, No. 5, pages 1 to 5 (Since the original is in English, it is described in Japanese)

(A8-1)

"It has been revealed that there is lanthanum carbonate including crystallization water in the form of not only three known forms of $La_2(CO_3)_3 \cdot H_2O$, $\cdot 3H_2O$, and $\cdot 8H_2O$ but also the form of $La_2(CO_3)_3 \cdot 5H_2O$." (Abstract, lines 1 to 3)

(A8-2)

"2.1 Synthesis of lanthanum carbonate

i) $La_2(CO_3)_3 \cdot 5H_2O$

Lanthanum oxide powder 200 mg was placed in a 4.3-cm long cylindrical glass container. Sodium chloride (1mg) and distilled water (100 ml) were added to the oxide.

A glass tube (an inner diameter φ of 5 mm) connected with a rubber tube was inserted into the solution, and carbon dioxide gas was blown through the tube at a rate of 2 ml/sec to dissolve the oxide. After blowing carbon dioxide into the solution for 48 hours, the precipitate was filtered, washed with carbonated water, and dried in the air

at about 15°C.

ii) $La_2(CO_3)_3 \cdot H_2O$, $\cdot 3H_2O$, $\cdot 8H_2O$

Processes for preparing these carbonates have been reported in previous literature.

a) $La_2(CO_3)_3 \cdot H_2O$

A definite amount of alkali metal carbonate was added to a lanthanum salt solution. Then, the obtained white precipitate was filtered, washed with carbonated water, and immediately dried in the air at 100°C.

b) $La_2(CO_3)_3 \cdot 3H_2O$

Carbon dioxide was blown into a lanthanum hydroxide suspension for 48 hours. The obtained precipitate was washed with acid water and vacuum-dried.

c) $La_2(CO_3)_3 \cdot 8H_2O$

A definite amount of sodium carbonate was added to a lanthanum salt solution. Then, the obtained precipitate was filtered, washed with carbonated water, and slowly dried at 20°C. Dehydration of trichloroic acid was also used as a common process for obtaining rare earth element crystals. In this experiment as well, $La_2(CO_3)_3 \cdot 8H_2O$ was obtained by the previous process." (page 1, line 7 from the bottom to page 2, line 18)

- A9: Isao Sugimoto et al., Solvates, Amorphous Solids, and Pharmaceutical Formulations, Journal of the Society of Powder Technology, 1985, Vol. 22, No. 2, pages 85 to 97

(A9-1)

" There are a large number of pharmaceutical products with crystallization water. Hydrates (including solvates) have different molecular formulas than their anhydrous ones and thus are often called pseudopolymorphs. In other words, they are often treated as a kind of polymorph in a broad sense. Hydrates may have polymorphisms themselves. When formulating pharmacological products that exist as hydrates, as in usual cases, it is necessary to accurately understand the differences in their physicochemical properties. In addition, phenomena, such as moisture absorption and dehydration, as well as the accompanying changes in physical properties and crystal form should be sufficiently studied as well." (page 86, left column, line 41 to right column, line 7)

(A9-2)

"For hydrates, it is important to have a clear understanding of their properties at

the prescription design stage, because crystallization water often affects quality control in the formulation process or the properties of the finished formulation." (page 86, right column, lines 23 to 26)

(A9-3)

"3.1 Problems in formulation

For hydrates, it is important to have a clear understanding of their properties at the prescription design stage, because crystallization water often affects the quality control in the formulation process or the properties of the finished formulation.

(1) Bioavailability

The bioavailability of oral preparations is greatly affected by solubility and dissolution rate. Shefter et al. state that the rate of hydrate dissolution theoretically decreases with increasing amount of crystallization water. In addition, it may be also affected by the physical properties of the powder, such as wettability, cohesiveness, and surface area. Erythromycin dihydrate shows higher solubility than monohydrate and anhydrate. For tetracycline, dihydrate showed higher bioavailability than trihydrate (Fig. 1). For ampicillin, it has been reported that there is a difference in absorption between anhydride and trihydrate, and it also has been reported that there is no difference between the two. In addition, many reports have stated that α-1 hydrate and β-1 hydrate showed different elution rates of fluprednisolone in vivo and in vitro.

(2) Chemical stability

For formulating a pharmaceutical product, it is preferable to select the crystalline form in a biologically advantageous manner as described in the previous section. It is also preferred that it is chemically and physically stable when formulated. In this sense, it is necessary to thoroughly study the difference in stability between polymorphs including hydrates.

The authors found that there are seven types of crystalline polymorphs and hydrates in cyanidanol, and that form II monohydrate is the most stable crystalline form among them under normal storage conditions. Figure 2 shows the stability of these polyforms and hydrates to light, and among them, form II monohydrate was the most stable. In addition, as a result of examining the effect of storage humidity, type II anhydride, type IV anhydride, and type I monohydrate, which are changed to light-unstable type I tetrahydrate by storage at high humidity, were unstable. ... (omitted) ...

(3) Physical stability

Crystallization water often has a great effect on the physical properties of the formulation itself.

According to experiments conducted by the authors, a comparative study of the disintegration behavior of berberine chloride tetrahydrate and dihydrate-containing tablets revealed that the tetrahydrate tablets disintegrate relatively quickly, whereas the dihydrate tablets are significantly inferior in disintegration. ... (omitted) ... It was considered that transforming the dihydrate to tetrahydrate in water causes the growth of tetrahydrate crystal on the crystal surface, which forms a network structure between the particles and results in interparticle bond formation. Consequently, the permeation of water into the tablet is slowed down, the dispersibility of the particles in water is deteriorated, thereby delaying the disintegration and elution." (page 86, right column, line 22 to page 88, right column, line 11)

- A15: Chemistry Dictionary Editing Committee, Ed., Chemistry Dictionary 5, Reduced edition, Kyoritsu Publishing Co., Ltd. published on November 15, 1963, page 735

(A15-1)

"Lanthanum carbonate Carbonated - (Omitted)

Process for preparation Alkali metal carbonate is added to an aqueous solution of lanthanum salt, and the resulting precipitate is dried at 100°C to give monohydrate or dried at room temperature to give octahydrate. Passing carbon dioxide through a suspension of hydroxide gives a trihydrate." (Page 735, right column)

4-3-2 Invention disclosed in A1

A According to the above A1-1 and A1-2, A1 is a document for "a phosphate ion-immobilizing agent consisting of a rare earth element carbonate or organic acid compound." As is evident from A1-13, it can be said that A1 discloses a phosphate ion-immobilizing agent using lanthanum carbonate monohydrate [$La_2(CO_3)_3 \cdot H_2O$] (A1-13) together with the experimental results of actually immobilizing phosphate.

B Also, according to A1-6 and A1-9, it can be said that the phosphate ion-immobilizing agent is based on the principle that an insoluble phosphate of a rare earth element is formed in the digestive system beyond the stomach of a living body and is excreted without any change from the body. According to A1-4 and A1-5, as prior arts, A1 discloses a method of treating hyperphosphatemia by oral administration of aluminum hydroxide and a method of using a zirconium compound as an adsorbent instead of aluminum hydroxide, and mentions the problems of the prior art particularly

when applied to a living body.

C Incidentally, A4, which is a technical document published in 1993, can be said to disclose that, as a practical measure against hyperphosphatemia, a phosphate binder is taken immediately after meals; in this practice, P contained in the diet and an adsorbent react with each other to form an insoluble compound, which makes it difficult for P to be absorbed from the intestinal tract, resulting in further decrease in P intake. (A4-1); and specific examples of phosphate binders include Almigel and calcium carbonate (A4-2). In addition, A5 is a printed book whose first edition was published in 1983 and ninth edition was published in 1988. A5 can be said to disclose that taking an aluminum preparation makes aluminum bind to phosphorus contained in food and make it unable to be absorbed through the intestine to prevent an increase in blood phosphorus concentration (A5-1). Then, the fact that phosphorus exists in the form of phosphoric acid in foods and in the body was a matter of common general technical knowledge at the time of the priority date of the patent application just as in the case of the description of Exhibit A6 in which three different Japanese terms "高リン血症 (blood disease with high phosphorus level)," "高リン酸血症(blood disease with high phosphoric acid level)," and "高リン酸塩血症(blood disease with high phosphate level)" are used for the same meaning as the term "hyperphosphatemia" in English. Therefore, it is obvious that phosphorus and P in the items shown in the above A4 and 5 mean phosphoric acid. According to these described matters, common general knowledge at the time of the priority date of the patent application includes that a phosphoric acid adsorbent, which is taken immediately after meals, binds to phosphoric acid contained in food to change the form thereof to one that prevents phosphoric acid from being absorbed from the intestine; and an increase in blood phosphate concentration can be prevented by taking the adsorbent. In other words, it can be said that the fact that hyperphosphatemia can be treated or prevented could have been common general knowledge at the time of the priority date of the patent application.

D Then, it can be said that A1 discloses the following invention (hereinafter, referred to as "Invention A1"

"A phosphate ion-immobilizing agent for the treatment or prevention of hyperphosphatemia comprising

lanthanum carbonate monohydrate."

4-3-3 Regarding Patent Invention 1

A　Comparison with Invention A1

According to A6-1, it would have been obvious to a person skilled in the art that the Japanese term "高リン血症(blood disease with high phosphorus level)" is synonymous with the Japanese term 高リン酸血症(blood disease with high phosphoric acid level)" and "高リン酸塩血症(blood disease with high phosphate level)", all used for the same meaning as the term "hyperphosphatemia" in English; and the "agent" for treatment or prevention of "高リン血症" or "高リン酸血症" can be used as a pharmaceutical composition.　In addition, the specification for the Patent (hereinafter, referred to as "the Patent specification") describes that "Throughout this specification the meaning of the term 'treatment' includes prevention." (page 4, column 7, from the bottom, lines 4 to 2).　Thus, the "treatment" in the Patent Invention 1 can be recognized to also include prevention.

Then, Patent Invention 1 and Invention A1 coincide in that each of them is

"a pharmaceutical composition for the treatment of hyperphosphatemia, comprising lanthanum carbonate represented by the following formula:

$La_2(CO_3)_3 \cdot xH_2O$" and

differ from each other in the following features.

(Different Feature 1)

Regarding the lanthanum carbonate represented by $La_2(CO_3)_3 \cdot xH_2O$, it is specified that x has a value of 3 to 6 in Patent Invention 1, whereas x is 1 in Invention A1.

(Different Feature 2)

Patent Invention 1 comprises lanthanum carbonate "in admixture or association with a pharmaceutically acceptable diluent or carrier," whereas Invention A1 does not specify that it is comprised in admixture or association with a diluent or carrier.

B　Judgment

(A) Regarding Different Feature 1

First, Different feature 1 is examined.

The above (Judgment 1) "(3)B" held that, at the priority date of the present application, since ▲1▼ lanthanum carbonate hydrates with different numbers of hydration water molecules can be obtained by adjusting the drying conditions, such as

drying temperature; and ▲2▼ in a medicament that exists as a hydrate, differences in the number of water molecules (hydration water) can affect the solubility, dissolution rate, and bioavailability of a medicinal substance and the chemical and physical stability of the medicament, it is common general technical knowledge or a well-known art to, during the development of the drug, investigate whether a compound under consideration forms a hydrate and, if the presence of a hydrate is confirmed, compare the compound with an anhydride or another hydrate of the same compound having a different number of hydration water molecules to prepare the optimum one." Furthermore, based on the fact that the phosphate ion extraction coefficient of lanthanum carbonate monohydrate of invention A1 is 90%, the above (Judgment 2) "(4)A" held that, "in light of the common general technical knowledge or well-known art at the time of the priority date of the present application recognized in the above (3)B, with respect to the lanthanum carbonate monohydrate (Invention A1) disclosed in A1, it is recognized that a person skilled in the art in contact with A1 could have been motivated to prepare lanthanum carbonate hydrates with different numbers of hydration water molecules in search of a phosphate ion-immobilizing agent with a higher phosphate ion extraction coefficient as well as excellent solubility, dissolution rate, chemical stability and physical stability;" and "it is recognized that a person skilled in the art could easily conceive of adjustment of drying conditions, such as the drying temperature to make the configuration of the lanthanum carbonate monohydrate (Invention A1) disclosed in A1 into the configuration of the lanthanum carbonate hydrate with the number of hydration water molecules in the range of 3 to 6. (the configuration of Patent Invention 1 relating to Different Feature 1)"

Therefore, a person skilled in the art could easily conceive of setting the number of hydration water molecules of lanthanum carbonate in the range of Patent Invention 1 to make it into the configuration of Invention 1 relating to Different Feature 1.

(B) Regarding Different Feature 2

Secondly, Different feature 2 is examined.

A1 includes no specific description about additive that is mixed or associated when the lanthanum carbonate monohydrate is actually made into a "pharmaceutical composition". However, as stated in Exhibit A7-1, it can be said that inclusion of various additives in addition to the active ingredient that acts as a drug in the pharmacological composition regardless of the dosage form or administration route was a matter of well-known prior art and almost essential in the production of pharmaceutical composition. Besides, E7 also specifies "dilution" as one of the

common roles of such additives of the pharmaceutical products. Furthermore, there are no particular circumstances, such as the inappropriate use of such additives in lanthanum carbonate.

Therefore, in Invention A1, comprising lanthanum carbonate "in admixture or association with a pharmaceutically acceptable diluent or carrier" is a matter which could be appropriately achieved by a person skilled in the art.

(C) Regarding effects

According to the above (Judgment 3) "A(B),"

the description of the Patent specification is found as "the percentage of phosphate removed at 5 minutes is 96.5% or 100% for $La_2(CO_3)_3 \cdot 4.4H_2O$ ('sample 3'), $La_2(CO_3)_3 \cdot 4H_2O$ ('sample 5'), and $La_2(CO_3)_3 \cdot 3.8\ H_2O$ ('sample 6'), which is higher than the percentage of phosphate removed for other lanthanum carbonate hydrates ('samples 1, 2, and 4') out of the scope of Invention 1," and the description of A1 is found as "the phosphate ion extraction coefficient of lanthanum carbonate monohydrate of Invention A1 is 90% at 2 hours after stirring in an aqueous solution adjusted to pH 7." Then, according to the above findings, both the test results for the lanthanum carbonate hydrate of the Patent Invention 1 and the experimental results for the lanthanum carbonate monohydrate of Invention A1 show the same kind of effect of "the percentage of phosphate removed" or "phosphate ion extraction coefficient." It can be said that the difference between the two experimental conditions is within the range of a design matter that could be appropriately performed by a person skilled in the art. When Invention A1 is configured to have the number of hydration water molecules of lanthanum carbonate monohydrate in the range of 3 to 6 and to be the configuration of Invention 1 relating to Different Feature 1, it is predictable that the value will be closer to 100% beyond the phosphate ion extraction coefficient (90%) of lanthanum carbonate monohydrate. It is therefore judged that the effect of the Patent Invention 1 could not be recognized as being far superior to the prediction of a person skilled in the art.

Regarding the diluent or carrier, which is the constituent element of the Patent Invention 1, the Patent specification includes no description about the results of experiments in the case of containing adiluent or carrier in the pharmaceutical composition. In other words, it cannot be confirmed that the pharmaceutical composition exerts more effects than those obtained by using a general diluent or carrier.

Therefore, Patent Invention 1 cannot be recognized as one that exerts a remarkable effect unpredictable by a person skilled in the art.

C Summary

As stated above, Patent Invention 1 could have been easily invented by a person skilled in the art based on Invention A1 and common general technical knowledge or well-known art.

4-3-4 Regarding Patent Inventions 2 to 8

Judgment by the body on Patent Inventions 2 to 8 is shown below.

4-3-4-1 Regarding Patent Inventions 2 and 3

A Comparison

Patent Invention 2 and Invention 3 specify the range of the number x of hydration water in Patent Invention 1 by limiting it to "x has a value from 3.5 to 5," and "x has a value from 3.8 to 4.5," respectively.

Then, Patent Inventions 2 and 3 are different from Invention A1 in the above Different Feature 2, and further are different respectively therefrom in the following Different Feature 1' and Different Feature 1".

(Different Feature 1') (Different Feature Between Patent Invention 2 and Invention A1)

Regarding the lanthanum carbonate represented by $La_2(CO_3)_3 \cdot xH_2O$, it is specified that x has a value of 3.5 to 5 in Patent Invention 2, whereas x is 1 in Invention A1.

(Different Feature 1") (Different Feature Between Patent Invention 3 and Invention A1)

Regarding the lanthanum carbonate represented by $La_2(CO_3)_3 \cdot xH_2O$, it is specified that x has a value of 3.8 to 4.5 in Patent Invention 2, whereas x is 1 in Invention A1.

B Judgment

The numerical range related to the above Different Feature 1' and Different Feature 1" is specified by further reducing the range of the number x of hydration water in Patent Invention 1.

As is evident from A1-13, A1 describes that the phosphate ion extraction coefficient was 90% under the conditions of stirring at pH 7 for 2 hours when lanthanum carbonate monohydrate was used in Example 11 at an addition amount of 0.5 g/l.

As forementioned in the above "4-3-3 B(A)," in light of the common general technical knowledge or well-known art at the time of the priority date of the present application certified in "(3) B," there is a motivation to try to prepare different numbers of hydration water molecules of lanthanum carbonate in order to obtain the phosphate ion-immobilizing agent of Invention A1 with a higher phosphate ion extraction coefficient and excellent characteristics. Then, A15 describes that lanthanum carbonate mono-, tri- and octahydrate can be obtained by a process for the preparation with drying temperature and precipitation (A15-1). A8 describes that "It has been revealed that there is lanthanum carbonate including crystallization water in the form of not only three known forms of $La_2(CO_3)_3 \cdot H_2O$, $\cdot 3H_2O$, and $\cdot 8H_2O$ but also the form of $La_2(CO_3)_3 \cdot 5H_2O$." in "Abstract," lines 1 to 3, and also concretely describes a process for preparing multiple hydrates in the section "2. Experimental." (A8-1 and A8-2).

From the descriptions in A15 and A8, it can be said that even though the lanthanum carbonate with the number of hydration water molecules of 3 or 5 and the preparation process thereof were known at the time of the priority date of the Patent, lanthanum carbonate with the number of hydration water molecules of 5 corresponds to one with x of 5 in the general formula of Patent Inventions 2 and 3 and lanthanum carbonate with the number of hydration water molecules of 3 corresponds to one with x of 3.

Then, it can be said that, when trying to prepare lanthanum carbonate with a different number of hydration water molecules in Invention A1 in search of a better phosphate ion-immobilizing agent, a person skilled in the art could easily conceive of using trihydrate and pentahydrate as indicators to consider one in which x is around 3 or 5 and setting the value of x to a range of 3.5 to 5 or 3.8 to 4.5, which is a range that includes or is close to the above known value.

Furthermore, as stated in the above "4-3-3 B(C)," the effect of lanthanum carbonate with the number of hydration water molecules of 3.8, 4, or 4.4 is not sufficiently significant to exceed the predictions of a person skilled in the art. Therefore, the effect of lanthanum carbonate with the number of hydration water molecules in the range of 3.5 to 5, or 3.8 to 4.5, which is included in them, is also not recognized to be remarkable that a person skilled in the art could not predict.

C Summary

Therefore, for the same reasons as forementioned in the above "4-3-3 B(A)," "4-3-3 B(B)," and "4-3-3 B(C)," Patent Inventions 2 and 3 could have been easily invented by a person skilled in the art based on Invention A1 and common general technical knowledge or well-known art.

4-3-4-2 Regarding Patent Invention 4

A Comparison

Patent Invention 4 is further specified as one "in a form suitable for oral administration" in any of Patent Inventions 1 to 3. Then, Patent Invention 4 and Invention A1 are different in terms of any of the above Different Feature 1, Different Feature 1' or Different Feature 1", and Different Feature 2, as well as different in terms of the following Different Feature 3.

(Different Feature 3)

Patent Invention 4 is specified as one "in a form suitable for oral administration," whereas Invention A1 is not specified as such.

B Judgment

As stated in the above "4-3-2 B," on the premise that there was a conventional technique for oral administration of adsorbent as a treatment for hyperphosphatemia and that the problem thereof was recognized, it can be said that A1 discloses that it uses the digestive system as the site of action, as it describes that a phosphate ion-immobilizing agent containing lanthanum carbonate forms insoluble phosphate in the digestive system beyond the stomach of the living body and the phosphate is excreted as it is from the body. A1-8 also describes that it is used in the form of being encapsulated with polysaccharides, such as gelatin and carrageenan. Thus, capsules using polysaccharides are one of the dosage forms suitable for oral administration.

Considering the foregoing, it can be said that A1 discloses that the phosphate ion-immobilizing agent is in "a form suitable for oral administration." Then, for formulating the phosphate ion-immobilizing agent of Invention A1, "a form suitable for oral administration" was conceivable without particular creativity by a person skilled in

the art.

Regarding oral administration of lanthanum carbonate, for demonstrating the lanthanum carbonate that is "fully excreted and does not pass out of the gut into the circulation system when given orally," the Patent specification describes that, as a result of excretion investigation after orally dosing three rats with lanthanum carbonate tetrahydrate, the amounts of lanthanum excreted from the rats after 72 hours were 103.3, 99.5, and 103.8 in terms of "%La Recovered," respectively, and lanthanum in the kidney, liver, and thigh of the rat after the test were analyzed and as a result all of them were less than 0.1 ppm (page 6, column 12, line 19 to page 7, column 14, last line and page 7, Table). However, as stated in the above "4-3-2 B," A1 describes the principle that the phosphate ion-immobilizing agent forms an insoluble phosphate of a rare earth element in the digestive system beyond the stomach of the living body and is excreted as it is from the body (A1-6 and A1-9). Thus, the above results are nothing but confirmations that the behavior of lanthanum carbonate tetrahydrate in the body does not violate this principle and thus does not exceed the prediction of a person skilled in the art.

C Summary

Therefore, for the same reasons as forementioned in the above "4-3-3 B(A)," "4-3-3 B(B)," "4-3-3 B(C)," and "4-3-4-1 B," Patent Invention 4 could have been easily invented by a person skilled in the art based on Invention A1 and common general technical knowledge or well-known art.

4-3-4-3 Regarding Patent Invention 5

A Comparison

Patent Invention 5 is further specified as one "in unit dosage form to provide from 0.1 to 20g/day" in any of Patent Inventions 1 to 4. Then, Patent Invention 5 that depends from any one of Patent Inventions 1 to 3 is different from Invention A1 in terms of any of the above Different Feature 1, Different Feature 1' or Different Feature 1", and Different Feature 2, as well as in terms of the following Different Feature 4. In addition, Patent Invention 5 that depends from Patent Invention 4 is different from Invention A1 in terms of any of the above Different Feature 1, Different Feature 1' or Different Feature 1", Different Feature 2, and Different Feature 3, as well as in terms of

the following Different Feature 4.

(Different Feature 4)

Patent Invention 5 is specified as one "in unit dosage form to provide from 0.1 to 20g/day," whereas Invention A1 is not specified as such.

B Judgment

A1 describes the dosage of the conventional adsorbent such that "oral administration of aluminum hydroxide usually requires 1 to 3 g to be taken 3 to 6 times a day, ... (Omitted) ... . However, the phosphorus adsorption capacity of the zirconium compound is similar to that of aluminum hydroxide, and the amount used cannot be reduced." (A1-4), and also describes the phosphate ion-immobilizing agent of Invention A1 such that "the immobilization performance of phosphate ions per unit weight is 5 times or more that of the conventional adsorbent method." (A1-6). In addition, although the dose of lanthanum carbonate monohydrate is not specifically described in A1, A1-10 describes cerium oxalate decahydrate as an example of "the phosphate ion-immobilizing agent of the present invention," and describes that it "requires less than the currently used dose of 3 to 6 g/day of aluminum hydroxide, and, at about 1 g/day, exerts a sufficient effect." Furthermore, A1-11 and A1-13 showed experiments of removing phosphate ions using 0.5 g/l of cerium oxalate decahydrate in Example 3 and 0.6 g/l of lanthanum carbonate monohydrate in Example 11. The obtained results indicate an extraction coefficient of 48% in Example 3 and an extraction coefficient of 90% in Example 11.

Considering the matters described in A1, in the first place, the dose of "0.1 to 20 g/day" in Patent Invention 5 is only a wide range that covers the dose of aluminum hydroxide, which is the prior art in which a large dose of the adsorbent is regarded as a problem. Then, comparing Example 3 and Example 11, in consideration of the fact that the lanthanum carbonate monohydrate exhibited a phosphate ion extraction coefficient equal to or higher than that of cerium oxalate decahydrate. it can be said that the lanthanum carbonate monohydrate of Invention A1 is also expected to be effective at the dose of "at about 1 g/day" presented for cerium oxalate decahydrate.

Furthermore, even if the Detailed Description of the Invention of the Patent specification is referred to, the test results for examining the action and effect related to the specific dose and the treatment of hyperphosphatemia on the living body are not shown. It is thus not recognized that the dose range of "0.1 to 20 g/day" has critical

significance. After all, therefore, the dose range of 0.1 to 20 g/day is only such that a person skilled in the art could set appropriately.

C Summary

Therefore, for the same reasons as forementioned in the above "4-3-3 B(A)," "4-3-3 B(B)," "4-3-3 B(C)," "4-3-4-1 B," and "4-3-4-2 B," Patent Invention 5 could have been easily invented by a person skilled in the art based on Invention A1 and common general technical knowledge or well-known art.

4-3-4-4 Regarding Patent Invention 6

A Comparison

Patent Invention 6 is an invention relating to the use of the lanthanum carbonate according to any one of Claims 1 to 3 for the preparation of a medicament for the treatment of hyperphosphatemia by administration into the gastrointestinal tract.

On the other hand, from the above "4-3-2 A," "4-3-2 B," and "4-3-2 C," it can be said that A1 describes the following invention (hereinafter, referred to as "Invention A1-A").

"The use of the lanthanum carbonate monohydrate for the preparation of the phosphate ion-immobilizing agent for the treatment of hyperphosphatemia"

As stated in the above "4-3-3 A," since different Japanese terms "高リン血症 (blood disease with high phosphorus level) and "高リン酸塩血症(blood disease with high phosphate level)" are used for the same meaning as the term "hyperphosphatemia" in English,

Patent Invention 6 and Invention A1 coincide in that each of them is "the use of lanthanum carbonate represented by $La_2(CO_3)_3 \cdot xH_2O$ for the preparation of a medicament for the treatment of hyperphosphatemia" and differ from each other in the following features.

(Different Feature A)

Regarding the lanthanum carbonate represented by $La_2(CO_3)_3 \cdot xH_2O$, it is specified that x has a value of 3 to 6, 3.5 to 5, or 3.8 to 4.5 in Patent Invention 6, whereas x is 1 in Invention A1.

(Different Feature 5)

The treatment is specified as "by administration into the gastrointestinal tract" in Patent Invention 6, but is not specified as such in Invention A1-A

B Judgment

Since Different Feature A is the same matter as Different Feature 1, Different Feature 1', or Different Feature 1", as forementioned in the above "4-3-3 B(A)," "4-3-3 B(C)," and "4-3-4-1 B," a person skilled in the art could easily conceive of setting x to 3 to 6, 3.5 to 5, or 3.8 to 4.5.

Considering the matter of "by administration into the gastrointestinal tract" related to Different Feature 5, as forementioned about Different Feature 3 in the above "4-3-4-2 B," it can be said that A1 discloses that the site of action of the phosphate ion-immobilizing agent is the digestive system and the agent is prepared to be suitable for oral administration. Therefore, there is no particular difficulty in making the treatment by administration into the gastrointestinal tract in Invention A1-A.

Also, regarding the effect of administration into the gastrointestinal tract, the Patent specification only shows the results of oral administration stated in the above "4-3-4-2 B." Thus, no evidence that the effect exceeds the expectations of a person skilled in the art could be found.

C Summary

Therefore, as forementioned in the above "4-3-3 B(A)", "4-3-3 B(C)", "4-3-4-1 B", and "4-3-4-2 B," Patent Invention 6 could have been easily invented by a person skilled in the art based on Invention A1-A and common general technical knowledge or well-known art.

4-3-4-5 Regarding Patent Invention 7

Patent Invention 7 is an invention of a process; i.e., a process for the preparation of pharmaceutical composition comprising lanthanum carbonate as defined in any one of Claims 1 to 3 which comprises the steps of:

(i) reacting lanthanum oxide with a hydrochloric acid to give lanthanum chloride;

(ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate;

(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of crystallization water; and

(iv) mixing the lanthanum carbonate obtained in step (iii) with a pharmaceutically acceptable diluent or carrier.

A Comparison

(A) As indicated in the above "4-3-2 A," according to A1-1 and A1-2, A1 is a document for "a phosphate ion-immobilizing agent consisting of a rare earth element carbonate or organic acid compound." Then, A1-13 describes that sodium carbonate aqueous solution was added to lanthanum chloride aqueous solution, and the resulting precipitate was filtered, washed with water, and dried at 100°C to prepare lanthanum carbonate monohydrate [$La_2(CO_3)_3 \cdot H_2O$]; and, using the obtained lanthanum carbonate monohydrate as a phosphate ion-immobilizing agent, 90% of phosphate ions were actually removed.

(B) Furthermore, as indicated in the above "4-3-2 B" according to A1-6 and A1-9, it can be said that the phosphate ion-immobilizing agent is based on the principle that an insoluble phosphate of a rare earth element is formed in the digestive system beyond the stomach of a living body and is excreted without any change from the body. A1-4 and A1-5, as prior arts, disclose a method of treating hyperphosphatemia by oral administration of aluminum hydroxide and a method of using a zirconium compound as an adsorbent instead of aluminum hydroxide, and mentions the problems of the prior art particularly when applied to a living body.

(C) Furthermore, as stated in the above "4-3-2 C," A4, which is a technical document published in 1993, can be said to disclose that, as a practical measure against hyperphosphatemia, a phosphate binder is taken immediately after meals; in this practice, P contained in the diet and an adsorbent react with each other to form an insoluble compound, which makes it difficult for P to be absorbed from the intestinal tract, resulting in further decrease in P intake (A4-1); and specific examples of phosphate binders include Almigel and calcium carbonate (A4-2). In addition, A5 is a printed book whose first edition was published in 1983 and ninth edition was published in 1988. A5 can be said to disclose that taking an aluminum preparation makes

aluminum bind to phosphorus contained in food and make it disable to be absorbed through the intestine to prevent an increase in blood phosphorus concentration (A5-1). Then, the fact that phosphorus exists in the form of phosphoric acid in foods and in the body was common general technical knowledge before the filing of the patent application just as in the case of the description of Exhibit A6 in which three different Japanese terms "高リン血症(blood disease with high phosphorus level)," "高リン酸血症(blood disease with high phosphoric acid level)," and "高リン酸塩血症(blood disease with high phosphate level)" are used for the same meaning as the term "hyperphosphatemia" in English. Therefore, it is obvious that phosphorus and P in the items shown in the above A4 and 5 mean phosphoric acid. According to these described matters, common general knowledge before the filing of the patent application includes that a phosphoric acid adsorbent, which is taken immediately after meals, binds to phosphoric acid contained in food to change the form thereof to one that prevents phosphoric acid from being absorbed from the intestine; and an increase in blood phosphate concentration can be prevented by taking the adsorbent. In other words, it can be said that the fact that hyperphosphatemia can be treated or prevented could be common general knowledge at the time of the priority date of the patent application.

(D) Then, it can be said that the following invention (hereinafter referred to as "Invention A1-B") is described in A1.

"A process for preparation of a phosphate ion-immobilizing agent for the treatment or prevention of hyperphosphatemia, wherein the agent comprises lanthanum carbonate monohydrate prepared by adding a sodium carbonate aqueous solution to a lanthanum chloride aqueous solution and then subjecting the generated precipitate to filtering and washing with water, followed by drying at 100°C.

(E) As stated in the above "4-3-3 A," it would have been obvious to a person skilled in the art that "a phosphate ion-immobilizing agent for the treatment or prevention of hyperphosphatemia" is used as "a pharmaceutical composition for the treatment of hyperphosphatemia."

In the following, Patent Invention 7 and Invention A1-B will be compared.

From the above description of A15-1, it is clear that the filtered, water-washed precipitate in Invention A1-B is a hydrate of lanthanum carbonate. Thus, "the generated precipitate" subjected to "filtering and washing" in Invention A1-B corresponds to "a wet cake," which is a hydrate of the lanthanum carbonate of Patent

Invention 7. In addition, the wording "drying at 100°C" of Invention A1-B means to control the temperature to dry to obtain lanthanum carbonate monohydrate, which is a lanthanum carbonate with one molecule of crystallization water.

Thus, Patent Invention 7 and Invention A1-B coincide in that each of them is "A process for preparation of a pharmaceutical composition for the treatment of hyperphosphatemia, comprising:
(ii) preparing a wet cake of a hydrate of lanthanum carbonate by reacting a solution of lanthanum chloride with sodium carbonate; and
(iii) control-drying the wet cake of the above lanthanum carbonate hydrate and drying it to obtain a lanthanum carbonate with a specific number of molecules of crystallization water,

wherein the composition comprises lanthanum carbonate obtained by step (iii)" and differ from each other in the following features.

(Different Feature B1)

Patent Invention 7 specifies that the step of obtaining lanthanum oxide is "reacting lanthanum oxide with hydrochloric acid" in step (i), whereas Invention A1-B does not specify step (i).

(Different Feature B2)

In Patent Invention 7, lanthanum carbonate octahydrate is obtained in step (ii), whereas in Invention A1-B a lanthanum carbonate without a specific number of molecules of crystallization water is obtained.

(Different Feature B3)

Patent Invention 7 is specified as "controlled drying ... to obtain a lanthanum carbonate with 3 to 6 molecules of crystallization water" in step (iii), whereas "control-drying" in Invention A1-B is to carry out drying at 100°C to attain a number of hydration water molecules of 1.

(Different Feature B4)

Patent Invention 7 has a step (iv) of mixing lanthanum carbonate with an acceptable diluent or carrier as a medicament, whereas Invention A1-B does not specify such a step.

B Judgment

The above-mentioned different features are examined.

(A) Regarding Different Feature B4

Step (iv) relating to Different Feature B4 is a step of mixing the active ingredient lanthanum carbonate hydrate with a diluent or carrier that is acceptable as a medicament in the process for the preparation of a pharmaceutical composition. As forementioned about Different Feature 2 in the above "4-3-3 B (B)," therefore, it is a matter which could be appropriately achieved by a person skilled in the art.

(B) Regarding Different Feature B1

Step (i) relating to Different Feature B1 is a step of preparing a lanthanum chloride solution for reaction with alkali metal carbonate. However, dissolving oxides in hydrochloric acid is just a common way to obtain chlorides, and reacting lanthanum oxide with hydrochloric acid to obtain lanthanum chloride is not a remarkable feature. Even with reference to Examples 1 and 2 described in the Detailed Description of the Invention of the Patent specification, the fact that the process of Example 2 using lanthanum oxide and hydrochloric acid is more preferable than other processes cannot be found.

(C) Regarding Different Feature B2 and Different Feature B3

The operation in each of steps (ii) and (iii) is to obtain "a lanthanum carbonate with 3 to 6 molecules of crystallization water" through "lanthanum carbonate octahydrate." However, "a lanthanum carbonate with 3 to 6 molecules of crystallization water" is nothing but lanthanum carbonate in which x is a value of 3 to 6 regarding to Different Feature 1.

As is evident from A1-13, A1 describes that the phosphate ion extraction coefficient was 90% under the conditions of stirring at pH 7 for 2 hours when lanthanum carbonate monohydrate was used in Example 11 at an addition amount of 0.5 g/l.

Regarding Different Feature 1, as stated in the above "4-3-3 B(A))," the above (Judgment 1) "(3)B" held that, at the priority date of the present application, since ▲1▼ lanthanum carbonate hydrates with different numbers of hydration water molecules can be obtained by adjusting the drying conditions, such as drying temperature; and ▲2▼ in a medicament that exists as a hydrate, differences in the number of water molecules (hydration water) can affect the solubility, dissolution rate, and bioavailability of a

medicinal substance and the chemical and physical stability of the medicament, it is common general technical knowledge or a matter of well-known art to, during the development of the drug, investigate whether a compound under consideration forms a hydrate and, if the presence of a hydrate is confirmed, compare the compound with an anhydride or another hydrate of the same compound having a different number of hydration water molecules to prepare the optimum one." Furthermore, the above (Judgment 2) "(4) A" held that, based on the fact that the phosphate ion extraction coefficient of lanthanum carbonate monohydrate of Invention A1 is 90%, "In light of the common general technical knowledge or well-known art at the time of the priority date of the present application recognized in the above (3)B, with respect to the lanthanum carbonate monohydrate (Invention A1) disclosed in A1, it is recognized that a person skilled in the art in contact with A1 could have been motivated to prepare lanthanum carbonate hydrates with different numbers of hydration water molecules in search of a phosphate ion-immobilizing agent with a higher phosphate ion extraction coefficient as well as excellent solubility, dissolution rate, chemical stability and physical stability." and "It is recognized that a person skilled in the art could easily conceive of adjustment of drying conditions, such as the drying temperature to make the configuration of the lanthanum carbonate monohydrate (Invention A1) disclosed in A1 into the configuration of the lanthanum carbonate hydrate with the number of hydration water molecules in the range of 3 to 6 (corresponding to the configuration of Invention 1 relating to Different Feature 1)."

Even in Invention A1-B, therefore, in light of the common general technical knowledge or well-known art certified in (Judgment 1) "(3) B," with respect to lanthanum carbonate monohydrate having a phosphate ion immobilization rate of 90%, it is recognized that a person skilled in the art could have been motivated to prepare lanthanum carbonate hydrates with different numbers of hydration water molecules in search of a phosphate ion-immobilizing agent with a higher phosphate ion extraction coefficient as well as excellent solubility, dissolution rate, chemical stability, and physical stability.

Furthermore, A8 describes that a precipitate was "slowly dried at 20°C" after washing, and $La_2(CO_3)_3 \cdot 3H_2O$ was "dried in the air at about 15°C" to obtain $La_2(CO_3)_3 \cdot 5H_2O$ (A8-2). Thus, it can be said that, at the time of the priority date of the Patent, the specific control conditions for drying to obtain lanthanum carbonate trihydrate and pentahydrate were also known as "▲1▼ lanthanum carbonate hydrates with different numbers of hydration water molecules can be obtained by adjusting the drying conditions, such as drying temperature," which is the common general technical

knowledge or well-known art certified by the above (Judgment 1) "(3)B."

Then, in Invention A1-B, it can be said that a person skilled in the art could easily conceive of "control-drying" a wet cake of lanthanum carbonate hydrate "to obtain a lanthanum carbonate with 3 to 6 molecules of crystallization water" with reference to lanthanum carbonate trihydrate and pentahydrate in attempting to prepare lanthanum carbonates with different numbers of hydration water molecules in search of better phosphate ion extraction coefficient and other properties for the lanthanum carbonate monohydrate having a phosphate ion extraction coefficient of 90%.

Furthermore, as is evident from A15-1, A15 describes that a lanthanum carbonate precipitate precipitated from an aqueous solution is dried at 100°C to obtain monohydrate or dried at room temperature to obtain octahydrate. In other words, it can be said that the precipitate, which is a wet cake, is dehydrated to monohydrate when dried under strong conditions or still dehydrated to octahydrate when dried under mild conditions. The fact that $La_2(CO_3)_3 \cdot 3H_2O$ was obtained by being "slowly dried at 20°C" and $La_2(CO_3)_3 \cdot 5H_2O$ was obtained by being "dried in the air at about 15°C" shows the same tendency as recognized from A15 in which, regarding the relationship between the strength of drying and the number of crystallization water of the resulting lanthanum carbonate, lanthanum carbonate with less crystallization water can be obtained by drying under strong conditions. From these matters, even if it is not specified in A1, it can be recognized that it naturally goes through the octahydrate state when lanthanum carbonate monohydrate is obtained by drying at 100°C in Invention A1-B, and similarly, even when crystallization water is reduced from octahydrate to carry out "controlled drying ... so as to obtain a lanthanum carbonate with 3 to 6 molecules of crystallization water," it naturally passes through the state of octahydrate.

Specifically, for preparing lanthanum carbonate by reaction of a solution of lanthanum chloride with an alkali metal carbonate, first of all, "a wet cake of octahydrate" is obtained at first. In this regard, with reference to the Detailed Description of the Invention of the Patent specification, there is the following description: "... . the present invention is a process for the preparation of lanthanum carbonate which comprises the steps of:

(i) reacting lanthanum oxide with an acid to give soluble lanthanum chloride;

(ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate;

and

(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to

obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallization." (page 2, column 4, pages 18 to 26). This description does not specify the acid used in step (i) as hydrochloric acid, and thus the same items as in the Patent Invention 7 are described except that the lanthanum salt solution in step (ii) is not specified as a lanthanum chloride solution. In addition, "standard commercial lanthanum carbonate, which is believed to be the octahydrate form" (page 2, column 3, line 50 to column 4, line 1) is described. However, it is not clear whether "standard commercial lanthanum carbonate, which is believed to be the octahydrate form" is obtained in the step (i). Therefore, it is not recognized that the Patent Invention 7 intends to use a specific commercial product as lanthanum carbonate octahydrate.

Furthermore, in the Detailed Description of the Invention of the Patent specification, Example 2 is described as "The process of Example 1 was repeated but using hydrochloric acid (12.28 M, 2.48 liters) in place of nitric acid to dissolve lanthanum oxide (1.5kg). ... . The product was divided in three approximately equal portions in Pyrex dishes and dried in a convection oven at 80°C. ... The time course of the drying process is shown below." (page 5, column 9, line 22 to column 10, line 24). The table following this description is shown below.

時　間	mol H_2O／La		
（時）	皿　1	皿　2	皿　3
2	21.3	22.1	20.4
5.5	12.3	13.2	12.2
9	7.9	8.0	7.6
11.5	6.9	7.0	6.6
17	4.9	5.1	4.6
18.5	4.6	4.8	4.2
19.5	4.4	4.6	4.1
20	4.3	4.6	4.0

時間（時）　Time (hours)
皿１　Dish 1
皿２　Dish 2

皿 3　　Dish 3

The above table shows the time variation of the value of "mol H_2O/La" up to 20 hours. The values after 20 hours are described as "4.3", "4.6", and "4.0" for the samples divided into three Pyrex dishes (Dish 1 to Dish 3), respectively. Here, according to the chemical formula $La_2(CO_3)_3 \cdot xH_2O$ of lanthanum carbonate, it can be said that hydration water x mol is the amount per 2 mol of La. The notation "mol H_2O/La" seems to represent that the value in Table 1 corresponds to 1/2 of the value of x in the above chemical formula. However, in the Detailed Description of the Invention of the Patent specification, the part following this table describes that " Measurement, Calculation regarding $La_2(CO_3)_3 \cdot 4H_2O$ (page 6, line 1)", "The XRD analysis for lanthanum carbonate $4H_2O$ prepared by the method of Example 2 is illustrated in Figure 3. ..." (page 6, column 11, lines 8 to 9), and so on. It is thus understood that the lanthanum carbonate finally obtained in Example 2 is the one with the number of hydration water molecules x = 4. Therefore, each of the values in the columns of "mol H_2O/La" is recognized to indicate the number of x in the formula $La_2(CO_3)_3 \cdot xH_2O$.

According to the above table, the value of "mol H_2O/La" decreases from the initial value exceeding 20 with the passage of time from drying. As the values at 9 hours, "7.9", "8.0", and "7.6" are described for Dishes 1 to 3, respectively. Then, the value changes from 0.1 to 0 from 19.5 hours to 20 hours after continuing to decrease gradually. As stated above, it shows a value of about 4 at 20 hours. In other words, it can be recognized that the octahydrate state was reached about 9 hours after the start of drying, followed by a further decrease in number of hydration water.

After all, even if Example 2 was examined, it was only confirmed "to produce a wet cake of lanthanum carbonate octahydrate" through the state of lanthanum carbonate octahydrate during drying from the wet state and nothing more than confirmation that lanthanum carbonate was changed to octahydrate. Also, it does not take any corresponding operation for being octahydrate when it is confirmed that lanthanum carbonate has become octahydrate. Therefore, "to produce a wet cake of lanthanum carbonate octahydrate ... controlled drying of the wet cake of lanthanum carbonate octahydrate" in Patent Invention 7 can be said to include drying the lanthanum carbonate obtained as a wet cake until the number of hydration water molecules becomes less than 8.

Then, as stated above, in the process for the preparation of Invention A1-B,

lanthanum carbonate goes through the state of octahydrate in the step of drying the lanthanum carbonate obtained as a precipitate. Therefore, Different Feature B2 cannot be said to be a substantial different feature. Similarly, when Invention A1-B is subjected to controlled drying to obtain a lanthanum carbonate with 3 to 6 molecules of crystallization water, it cannot be a substantial different feature.

(D) Regarding effects

As stated in the above "4-3-3 B(C)," the effect of lanthanum carbonate with the number of hydration water molecules of 3 to 6 is not recognized to be far superior to the prediction of a person skilled in the art. In addition, the Detailed Description of the Invention of the Patent specification does not show the results when mixed with a diluent or carrier that is acceptable as a medicine. Furthermore, for example, the comparison result between the process for the preparation including steps (i) and (ii) and any of other processes for the preparation is not shown. There is no evidence that the process for the preparation of the Patent Invention 7 has a remarkable effect in obtaining a pharmacological composition compared to other processes for the preparation.

C Summary

Therefore, for the same reasons as forementioned in the above "4-3-3 B(A)," "4-3-3 B(B)," "4-3-3 B(C)," and "4-3-4-1 B," Patent Invention 7 could have been easily invented by a person skilled in the art based on Invention A1 and common general technical knowledge or well-known art.

4-3-4-6 Regarding Patent Invention 8

A Comparison

Patent Invention 8 is an invention relating to the use of the lanthanum carbonate according to any one of Claims 1 to 3 for the preparation of a medicament for the treatment of hyperphosphatemia in a patient with renal failure.

On the other hand, as stated in the above "4-3-4-4 A," from the above "4-3-2 A," "4-3-2 B," and "4-3-2 C," it can be said that A1-A describes the following invention.

"The use of the lanthanum carbonate monohydrate for the preparation of the phosphate ion-immobilizing agent for the treatment of hyperphosphatemia"

As stated in the above "4-3-3 A," since different Japanese terms "高リン血症 (blood disease with high phosphorus level) and "高リン酸塩血症(blood disease with high phosphate level)" are used for the same meaning as the term "hyperphosphatemia" in English,

Patent Invention 8 and Invention A1-A coincide in that each of them is "the use of lanthanum carbonate represented by $La_2(CO_3)_3 \cdot xH_2O$ for the preparation of a medicament for the treatment of hyperphosphatemia" and differ from each other in the following features.

(Different Feature A)

Regarding the lanthanum carbonate represented by $La_2(CO_3)_3 \cdot xH_2O$, it is specified that x has a value of 3 to 6, 3.5 to 5, or 3.8 to 4.5 in Patent Invention 8, whereas x is 1 in Invention A1-A.

(Different Feature 6)

Patent Invention 8 specifies that hyperphosphatemia to be treated is "in patient with renal failure", whereas Invention A1-A is not specified as such.

B Judgment

Since Different Feature A is the same matter as Different Feature 1, Different Feature 1', or Different Feature 1", as forementioned in the above "4-3-3 B(A)," "4-3-3 B(C)," and "4-3-4-1 B," a person skilled in the art could easily conceive of setting x to 3 to 6, 3.5 to 5, or 3.8 to 4.5 in Invention A1-A.

As is evident from A1-4, A1 describes that "It is well known that in patients with chronic renal failure, hyperphosphatemia is caused by impaired excretion of phosphorus." In Invention A1-A, it can be said that the treatment targets include hyperphosphatemia in patients with renal failure. Thus, a person skilled in the art could appropriately specify the hyperphosphatemia to be treated only for patients with renal failure. In addition, the Patent specification does not describe administration examples for patients. There is no evidence that, for example, hyperphosphatemia has a special effect when it is used in patients with renal failure.

C Summary

Therefore, for the same reasons as forementioned in the above "4-3-3 B(A)," "4-3-3 B(C)," and "4-3-4-1 B," Patent Invention 8 could have been easily invented by a person skilled in the art based on Invention A1 and common general technical knowledge or well-known art.

4-3-5 The Demandee's allegation

A The Demandee roughly alleges as the following [A] to [C] in the written answer, oral proceedings statement brief, and written statement to make rebuttal statements on the reason for invalidation 3 alleged by the Demandant.

[A] Considering the examples described in A1, lanthanum is used in only one example, Example 11, among 14 examples. Moreover, it is an example of using a monohydrate that is not included in the range of Patent Invention 1. Considering the measured phosphate ion extraction coefficient, the examples using cerium, neodymium, gadolinium, and samarium gave better phosphate ion extraction coefficients than did Example 11 using lanthanum. Thus, a person skilled in the art in light of A1 would not have tried to investigate the lanthanum, which had a lower phosphate ion extraction coefficient than cerium. ("Gadolium" in the original text is recognized as a misspelling of "gadolinium".)

[B] In A1, there is no finding that the phosphate ion extraction coefficient varies as the hydration number is changed for a specific metal hydrate salt and thus there is no motivation to change the scope of hydrate.

[C] In the phosphate (salt)-binding capability of lanthanum carbonate, shown in Figure 1 and Table 1 of the Patent publication, for the number x of hydration water, Samples 3, 5, and 6 with x = 4.4, x = 4.0 and x = 3.8 showed high percentages of phosphate removed after 5 minutes under the condition of pH 3 , such as 96.5%, 100%, and 100%, respectively. On the other hand, in the case of Sample 2 with x = 1.3, which corresponds to the lanthanum carbonate monohydrate of A1, the percentage of phosphate removed after 5 minutes was as low as 39.9%. In A1, the phosphate ion extraction coefficient of lanthanum is inferior to that of cerium, neodymium, or the like. Therefore, it was a completely unexpected and remarkable effect that the different numbers of hydration water molecules showed higher values as described above.

It is also completely unexpected that lanthanum carbonate, which has a specific hydration number under the same environment as the stomach of pH 3, showed excellent phosphate (salt)-binding capability as early as 5 minutes later. Then, since the medicine is administered together with food and must combine with phosphate (salt) before it can be absorbed into the bloodstream, it is very important to bind with phosphate (salt) under acidic conditions of the stomach in an early stage.

The Demandant submitted an experimental report and alleged that the Patent Invention 1 has no remarkable effect as the phosphate ion extraction coefficient of lanthanum carbonate octahydrate exceeds or is equal to those of the samples included in the scope of the Patent Invention. However, lanthanum carbonate octahydrate is not described in A1 and such a comparison does not have influence on the inventive step over the invention disclosed in A1.

In addition, lanthanum carbonate pentahydrate, hexahydrate, trihydrate, and octahydrate are described in A13, A14 and A15, respectively. However, A13 to A15 do not mention the relationship with the treatment of hyperphosphatemia, let alone the phosphate ion extraction coefficient.

Furthermore, the formulations of Invention for the Patent have been extremely successful in commerce, and such success should be taken into account to support the inventive step of the Patent Invention.

B The above allegation is examined.

Regarding [A]

According to A1-11 to A1-14, in Examples 1 to 14 of A1, the results of examining the phosphate ion extraction coefficient under the conditions of pH 7 and stirring for 2 hours are shown for carbonate or organic acid compounds of various rare earth elements. The results are summarized below. In Example 5, just as in the case of Example 1, cerium oxalate decahydrate was added in an amount of 1.0 g/l. Example 5 describes that the chloride ion concentration and the carbonate ion concentration, which are not mentioned in Example 1, are 85 mM/l and 48 mM/l, respectively. In addition, although cerium is also described as "the first cerium" in the examples of A1, it is simply described as "cerium" here.

	Added amount (g/l)	Extraction coefficient (%)

Cerium oxalate decahydrate	1.0	99 (Example 1)
Cerium oxalate decahydrate	0.2	19 (Example 2)
Cerium oxalate decahydrate	0.5	48 (Example 3)
Cerium oxalate decahydrate	1.5	100 (Example 4)
Cerium oxalate decahydrate	1.0	97 (Example 5)
Cerium carbonate 9-hydrate	0.5	98 (Example 6)
Sodium cerium carbonate 6-hydrate	1.0	93 (Example 7)
Cerium citrate 3.5-hydrate	0.5	92 (Example 8)
Cerium malonate 6-hydrate	1.0	100(Example 9)
Yttrium carbonate 3-hydrate	0.5	85 (Example 10)
Lanthanum carbonate monohydrate	0.6	90 (Example 11)
Neodymium oxalate 10-hydrate	1.0	97 (Example 12)
Gadolinium oxalate 10 hydroxide	1.0	92 (Example 13)
Samarium oxalate decahydrate	1.0	91 (Example 14)

From the above results, simple comparison of the values of extraction coefficients resulted in that, as the Demandee states, the value of the phosphate ion extraction coefficient by lanthanum carbonate monohydrate in Example 11 was inferior than those of the oxalates of neodymium, gadolinium, and samarium in Examples 12 to 14 and the cerium compounds in Examples 1 and 4 to 9. However, the ability of phosphate ion-immobilizing agents to remove phosphate ions is related to the amount of fixative required to remove phosphate ions. Therefore, it is necessary to evaluate the added amount of each compound as well. Considering the results of the examples from this point of view, it can be recognized that [1] in the other examples, most of the results were the results of the added amount of 1.0 g/l, whereas in Example 11, the results were the added amount of 0.6 g/l; [2] the results of Example 3 (cerium oxalate decahydrate 0.5 g/l), Example 6 (Cerium carbonate 9-hydrate 0.5 g/l), Example 8 (Cerium citrate 3.5-hydrate 0.5 g/l), and Example 10 (Yttrium carbonate 3-hydrate 0.5 g/l) are 48%, 98%, 92% and 85%, respectively, which are close to the result of Example 11, and thus it cannot be said that the result of lanthanum carbonate monohydrate in Example 11 is particularly inferior among the examples in which the added amounts are close to each other; and [3] the extraction coefficients are 93%, 92% and 91%, respectively in Example 7 (Cerium carbonate 6-hydrate), Example 13 (Gadolinium oxalate 10 hydroxide), and Example 14 (samarium oxalate) in which the added amount was 1.0 g/l, , but are not significantly different from the extraction coefficient of 90% in Example 11 in spite of their different added amounts.

Then, it cannot be said that lanthanum carbonate monohydrate is inferior to other compounds of various rare earth elements described in A1. Thus, a person skilled in the art in contact with A1 could naturally consider lanthanum carbonate monohydrate.

Regarding [B]

As alleged by the Demandee, there is no particular suggestion in A1 about changing the number of hydration water molecules of lanthanum carbonate monohydrate. However, as stated in (Judgment 1), in light of which it was common general technical knowledge and well-known at the time of the priority date of the present application that "lanthanum carbonate hydrates with different numbers of hydration water molecules can be obtained by adjusting the drying conditions, such as drying temperature" and "in a medicament that exists as a hydrate, ... if the presence of a hydrate is confirmed and compare the compound with an anhydride or another hydrate of the same compound with a different number of hydration water molecules to prepare the optimum one," it is recognized that a person skilled in the art in contact with A1 could have been motivated to prepare lanthanum carbonate hydrates with different numbers of hydration water molecules in search of lanthanum carbonate monohydrate with excellent characteristics as a medicament. The lack of teaching in A1 itself about changing the number of hydration water molecules of lanthanum carbonate is not grounds for denying this motivation.

Regarding [C]

The effect of setting the number of hydration water molecules of lanthanum carbonate hydrate to 3 to 6 is as forementioned in the above 4-3-3 B(C). According to "A (B)" in the above (Judgment 5), it cannot be admitted to be far superior to the prediction of a person skilled in the art.

In addition, the commercial success of the Patent Invention product is not directly related to the judgment of inventive step.

C Summary

Therefore, none of the Demandee's allegations on reason for invalidation 3 can be accepted.

No. 5 Closing

As stated above, the Patent for the Patent Inventions 1 to 8 violates the provision of Article 29(2) of the Patent Act and thus falls under Article 123(1)(ii) of the Patent Act. Therefore, the Patent should be invalidated without having to judge other reasons for invalidation alleged by the Demandant.

The costs in connection with the trial shall be borne by the Demandee under the provisions of Article 61 of the Code of Civil Procedure which is applied mutatis mutandis in the provisions of Article 169(2) of the Patent Act.

Therefore, the trial decision shall be made as described in the conclusion.

October 16, 2019

Chief administrative judge: MITSUMOTO, Minako
Administrative judge: INOUE, Noriyuki
Administrative judge: FUJIWARA, Hiroko