Patent Right	Date	May 17, 2021	Court	Intellectual Property High Court, Third Division
	Case number	2020 (Gyo-Ke) 10015		
- A case in which the court determined that the determination of a trial decision contains no error in that it found a matter required to identify an invention pertaining to the effect of the invention and affirmed involvement of an inventive step in the invention on the grounds that a person skilled in the art could not have easily conceived of said matter.				

Case type: Rescission of Trial Decision to Maintain
Results: Dismissed
References: Article 29, paragraph (2) of the Patent Act
Related rights, etc.: Patent No. 6192115
Trial decision: Invalidation Trial No. 2018-800090

Summary of the Judgment

1. This case is an action to seek rescission of a trial decision to dismiss a request for a trial for invalidation of a patent pertaining to the Invention titled "Novel formulation which stabilizes immunogenic compositions and inhibits precipitation." The Invention comprises the following structures (partially simplified):

"A formulation put in a siliconized container, which inhibits the silicon-induced aggregation of polysaccharide-protein conjugates contained in a siliconized container;
(i) which is a formulation containing pH buffered salt solution, wherein said buffer has a pKa of from about 3.5 to about 7.5;
(ii) aluminum salt; and
(iii) conjugates of pneumococcal polysaccharide of 13 types of serotypes and CRM_{197} polypeptide."
("Conjugates of pneumococcal polysaccharide and CRM_{197} polypeptide" are hereinafter referred to as "pneumococcal CRM conjugates.")

The cited invention found in the trial decision is an invention found from a medicinal formulation that had already been made available in the market as of the priority date of the Patent. The cited invention was identical with the Invention in terms of (ii) above but differed from the Invention in terms of (iii) above in that they are both pneumococcal CRM conjugates but the cited invention contained only seven types of serotypes (7-valent) (Difference 1). In addition, the cited invention does not contain the matter required to identify the Invention, "inhibiting aggregation induced by silicone"

(Difference 4).

In the trial decision, the JPO determined that a person skilled in the art could not have easily conceived of any of the structures of the Invention pertaining to the aforementioned differences and concluded that the Invention cannot be considered to lack an inventive step and that the request for a trial for invalidation is to be dismissed.

2. In this judgment, the court dismissed the Plaintiff's claim on the grounds that the determination of the trial decision contains no error. In this judgment, the summary of the determination concerning whether a person skilled in the art could have easily conceived of Difference 4 is as follows.

(1) Concerning the technical significance of the matter required to identify the invention pertaining to Difference 4

In light of the statements in the Description, the technical significance of the matter required to identify the invention, i.e., that the formulation of the Invention produces the effect of inhibiting silicon-induced aggregation, is understood as follows.

[i] Free pneumococcal conjugates play a part in silicon-induced aggregation, irrespective of the serotype of pneumococcal bacteria.

[ii] The formulation of the Invention has a composition comprising (i) to (iii), and as a result, in a solution, pneumococcal CRM conjugates and aluminum salt are bound to each other and the amount of free pneumococcal CRM conjugates is relatively reduced.

[iii] As a result of being in the state mentioned in [ii] above, silicon-induced aggregation based on the principle mentioned in [i] above is inhibited.

(2) Concerning the technical significance of the cited invention

Product information about the formulation of the cited invention (hereinafter referred to as "7-valent Prevenar") contains statements that in the same formulation, 7-valent pneumococcal CRM conjugates are absorbed on aluminum salt. However, it contains no statement that discloses or suggests the technical significance of absorption on aluminum salt. In addition, no statement concerning said technical significance can be found in documents in the evidence on this case.

(3) Whether a person skilled in the art could have easily conceived of Difference 4

As mentioned in (1) above, the matter required to identify the Invention pertaining to Difference 4, that is, "inhibiting the silicon-induced aggregation of polysaccharide-protein conjugates contained in a siliconized container," means that silicon-induced aggregation in which free pneumococcal CRM conjugates play a part is inhibited because of being in the condition in which pneumococcal CRM conjugates and aluminum salt are bound to each other and the amount of free pneumococcal CRM conjugates in the solution is reduced to the intended amount.

On the other hand, according to (2) above, it can be said that when seeing product information about 7-valent Prevenar, a person skilled in the art only recognizes that pneumococcal CRM conjugates absorbed on aluminum salt are contained in 7-valent Prevenar and that it was not easy for a person skilled in the art to recognize whether free pneumococcal conjugates exist in the solution of 7-valent Prevenar and the amount thereof in relation to the problem of silicone aggregation in which free pneumococcal conjugates play a part. In addition, the amount of free pneumococcal CRM conjugates in the formulation of the Invention can differ depending on the amount of pneumococcal CRM conjugates having six types of serotypes added to 7-valent Prevenar and also differs depending on the absorbability on aluminum salt of each of the serotypes added. Therefore, a person skilled in the art cannot even predict whether free pneumococcal CRM conjugates exist in the solution of a formulation having the composition of the Invention based on the cited invention. As a result, a person skilled in the art also cannot predict whether silicon-induced aggregation in which free pneumococcal CRM conjugates play a part is inhibited by a formulation having the composition of the Invention.

For the reasons described above, based on the cited invention, a person skilled in the art could not have easily conceived of the matter required to identify the invention pertaining to Difference 4, that is, the point that a formulation has a composition comprising (i) to (iii) in order to inhibit the silicon-induced aggregation of pneumococcal CRM conjugates in a siliconized container.

(4) Concerning the Plaintiff's allegations

A. Concerning the allegation that Difference 4 is not a substantial difference

The Plaintiff alleges as follows: Difference 4 is substantially a common feature and is not a difference, taking into account that when seeing product information about 7-valent Prevenar, a person skilled in the art understood that silicon-induced aggregation is also inhibited in 7-valent Prevenar for some reason and that inhibition of silicon-induced aggregation by aluminum phosphate that occurred in 7-valent Prevenar also naturally occurs in 13-valent pneumococcal CRM conjugates, putting aside the degree of inhibition.

However, the statement, "(t)he vaccine should … be inspected visually for any particulate matter and/or variation of physical aspect prior to administration," in product information about 7-valent Prevenar can also be understood as an instruction to confirm whether the vaccine has not changed in quality due to a defect in manufacturing or storage as a general precaution for the use of a medicine for injection. Therefore, it cannot be necessarily said that, when seeing said statement, a person

skilled in the art at the time of the Priority Date, when there was no knowledge about the silicon aggregation of polysaccharide-protein conjugates, could understand that aggregation can be formed but is ordinarily inhibited, as alleged by the Plaintiff. Furthermore, it must be said that it is difficult for such person skilled in the art to determine whether such aggregation is induced by silicone. On the other hand, the Invention clearly identifies the cause of aggregation of 13-valent pneumococcal CRM conjugates as induction by silicone and then states inhibition of such aggregation as a matter required to identify the invention. Therefore, in this regard, the Invention can be considered to be different from the cited invention.

Consequently, the trial decision contains no error in having found Difference 4, and the aforementioned allegation of the Plaintiff is not acceptable.

B. Concerning the easiness of discovering the problem, that is, inhibition of silicon-induced aggregation

The Plaintiff alleges as follows: silicon-induced aggregation in protein formulations had been known, and persons skilled in the art had understood that protein aggregation is the driving force for polysaccharide-protein conjugate aggregation; therefore, persons skilled in the art could predict that silicon-induced aggregation is formed in a 13-valent pneumococcal CRM conjugate formulation, in which the protein content is increased by adding six types of serotypes of pneumococcal CRM conjugates to the cited invention.

However, publicly known documents used by the Plaintiff as grounds for its allegation only contain statements about aggregation associated with the structural instability of polysaccharide-protein conjugates. Therefore, it cannot be said that silicon-induced aggregation of polysaccharide-protein conjugates had been recognized by persons skilled in the art as a problem at the time of the Priority Date based on these publicly known documents.

Therefore, the aforementioned allegation of the Plaintiff is not acceptable.

Judgment rendered on May 17, 2021
2020 (Gyo-Ke) 10015, Case of seeking rescission of the JPO decision
Date of conclusion of oral argument: March 10, 2021

Judgment

Plaintiff: Merck Sharp & Dohme Corp.

Defendant: Wyeth LLC

Main text

1. The Plaintiff's claim shall be dismissed.
2. The Plaintiff shall bear the court costs.
3. For the Plaintiff, the additional period for filing a final appeal and a petition for acceptance of final appeal with respect to this judgment shall be 30 days.

Facts and reasons

No. 1 Claim

The decision made by the Japan Patent Office (JPO) on October 3, 2019, concerning Invalidation Trial No. 2018-800090 shall be rescinded.

No. 2 Outline of the case

1. Outline of procedures at the JPO

(1) The Defendant is the patentee of Patent No. 6192115 (hereinafter referred to as the "Patent") for an invention titled "Novel formulation which stabilizes immunogenic compositions and inhibits precipitation."

The Patent is related to Patent Application No. 2014-144436, which was filed on July 14, 2014, by making part of Patent Application No. 2009-507900, for which international filing date is April 19, 2007 (priority claim under the Paris Convention accepted by a foreign office: April 26, 2006: the United States), into a new patent application, and the establishment of the patent right was registered on August 18, 2017.

(2) On July 13, 2018, the Plaintiff filed a request for a trial for invalidation with regard to all the claims of the Patent (Invalidation Trial No. 2018-800090).

On October 3, 2019, the JPO rendered a trial decision to maintain the Patent (hereinafter referred to as the "Trial Decision"), and a certified copy thereof was delivered

to the Plaintiff on October 11, 2019. Incidentally, 90 days were added as the statute of limitations for filing an action.

(3) On February 7, 2020, the Plaintiff filed an action to seek rescission of the Trial Decision.

2. Statement of the claims

The Patent comprises 22 claims, and all of Claims 2 to 22 are the dependent claims of Claim 1.

Claim 1 is stated as follows (hereinafter referred to as the "Invention").

[Claim 1]

A formulation put in a siliconized container, which inhibits the silicon-induced aggregation of polysaccharide-protein conjugates contained in a siliconized container;

(i) which is a formulation containing pH buffered salt solution, wherein said buffer has a pKa of from about 3.5 to about 7.5;

(ii) aluminum salt; and

(iii) polysaccharide-protein conjugates containing S. pneumoniae serotype 4 polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 6B polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 9V polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 14 polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 18C polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 19F polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 23F polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 1 polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 3 polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 5 polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 6A polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 7F polysaccharide conjugated to CRM_{197} polypeptide, and

S. pneumoniae serotype 19A polysaccharide conjugated to CRM_{197} polypeptide

3. Summary of the reasons for the Trial Decision

The ground for rescission of the Trial Decision alleged by the Plaintiff in this action is an error in the determination of the Trial Decision concerning involvement of an inventive step in the Invention. Therefore, the summary of said determination is indicated below.

(1) Cited invention

The following invention (hereinafter referred to as "Publicly Known Invention 1") had been publicly known to be worked in a foreign country prior to the priority date of

the Patent. Incidentally, Publicly Known Invention 1 is an invention that is found from a vaccine formulation that had been available in the market under the trade name of "Prevenar." The same formulation is hereinafter sometimes referred to as "7-valent Prevenar" as it is effective for seven types of pneumococcal bacteria.

"A vaccine formulation of pneumococcal polysaccharide-protein conjugates contained in a glass vial with a butyl rubber stopper or a glass prefilled syringe with a plunger bar, which is put in a glass vial with a butyl rubber stopper or a glass prefilled syringe with a plunger bar;

(i) which is a vaccine formulation containing sodium chloride solution;

(ii) aluminum phosphate; and

(iii) polysaccharide-protein conjugates containing 2μg pneumococcal polysaccharide serotype 4 conjugated to CRM_{197} carrier protein,

4μg pneumococcal polysaccharide serotype 6B conjugated to CRM_{197} carrier protein,

2μg pneumococcal polysaccharide serotype 9V conjugated to CRM_{197} carrier protein,

2μg pneumococcal polysaccharide serotype 14 conjugated to CRM_{197} carrier protein,

2μg pneumococcal polysaccharide serotype 18C conjugated to CRM_{197} carrier protein,

2μg pneumococcal polysaccharide serotype 19F conjugated to CRM_{197} carrier protein, and

2μg pneumococcal polysaccharide serotype 23F conjugated to CRM_{197} carrier protein"

(2) Common features

"A formulation of polysaccharide-protein conjugates contained in a container, which is put in a container;

(ii) which is a formulation containing aluminum salt; and

(iii) polysaccharide-protein conjugates containing S. pneumoniae serotype 4 polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 6B polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 9V polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 14 polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 18C polysaccharide conjugated to CRM_{197} polypeptide,

S. pneumoniae serotype 19F polysaccharide conjugated to CRM_{197} polypeptide, and

S. pneumoniae serotype 23F polysaccharide conjugated to CRM_{197} polypeptide"

(3) Differences

(Difference 1)

Regarding pneumococcal polysaccharide-protein conjugates (hereinafter merely referred to as "pneumococcal conjugates"), the Invention contains 13 types of pneumococcal conjugates mentioned in 2. Above (13-valent). On the other hand, Publicly

Known Invention 1 is a vaccine formulation containing seven types of pneumococcal conjugates mentioned in (1) above (7-valent).

(Difference 2)

The Invention contains "pH buffered salt solution, wherein said buffer has a pKa of from about 3.5 to about 7.5." On the other hand, Publicly Known Invention 1 does not contain such solution.

(Difference 3)

In the Invention, the container is a "siliconized" container. On the other hand, in Publicly Known Invention 1, it is not clear whether a glass vial with a butyl rubber stopper or a glass prefilled syringe with a plunger bar is "siliconized."

(Difference 4)

In the Invention, the formulation "inhibits the silicon-induced aggregation of polysaccharide-protein conjugates contained in a siliconized container." On the other hand, Publicly Known Invention 1 is not identified as such.

(4) Concerning Difference 1

A. It is found that persons skilled in the art had known that a 13-valent pneumococcal conjugate vaccine is formulated by adding serotypes 1, 3, 5, 6A, 7F, and 19A to a 7-valent pneumococcal conjugate vaccine and comprises serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

On that basis, it can be said that persons skilled in the art had a motivation to develop a 13-valent pneumococcal conjugate vaccine by adding serotypes 1, 3, 5, 6A, 7F, and 19A to the 7-valent pneumococcal conjugate vaccine of Publicly Known Invention 1.

B. However, in light of the following points, it is rather avoided to choose only CRM_{197} (hereinafter merely referred to as "CRM") as carrier protein that is bound to 13-valent pneumococcal polysaccharide in anticipation of the possibility of use as a formulation (vaccine). Therefore, it can be said that a person skilled in the art could not have easily conceived of it.

(A) No publicly known document includes a statement suggesting that a composition containing conjugates made by conjugating 13-valent pneumococcal polysaccharide to CRM (hereinafter merely referred to as "pneumococcal CRM conjugates") can actually be used as a vaccine formulation. In addition, taking into account that multiple proteins are well-known as proteins that can become the carrier proteins of a multi-value conjugate vaccine and that it is also well-known that more than two types of those proteins can be used in combination, many types of proteins can be candidates for the carrier protein of a 13-valent pneumococcal conjugate vaccine. Therefore, none of the statements in publicly known documents can be considered to suggest to persons skilled in the art to choose only

CRM as carrier protein to be used for obtaining a 13-valent pneumococcal conjugate vaccine.

Incidentally, there were publicly known documents stating that a composition containing 9-valent pneumococcal CRM conjugates is at the Phase III trial stage or that said composition is immunogenic. However, it is not found that it was common practice to adopt the same carrier protein as that adopted in a lower-valent conjugate vaccine for a higher-valent conjugate composition, and it was not common general technical knowledge that a high-valent conjugate composition is also expected to have an effect as a formulation (vaccine) if adopting the same carrier protein as that adopted in a lower-valent conjugate vaccine. Therefore, it cannot be said that statements in the aforementioned publicly known documents had suggested to persons skilled in the art to choose only CRM as carrier protein in a 13-valent pneumococcal conjugate vaccine. Moreover, there was also a publicly known document stating that an 11-valent pneumococcal CRM conjugate vaccine is at the "preclinical" stage. However, it cannot be said that said publicly known document discloses an 11-valent pneumococcal conjugate vaccine because the statement using the term "preclinical" does not clearly indicate its utility as a vaccine formulation.

(B) There is a publicly known document including statements disclosing awareness of a problem that in expanding the scope of protection of serum, use of a single carrier protein in a pneumococcal conjugate vaccine may cause overload of the carrier and may deteriorate immune response and also disclosing the fact that two types of carrier proteins (DT and TT) were used in an 11-valent pneumococcal conjugate vaccine to solve that problem. These statements suggest that persons skilled in the art considered that multiple carrier proteins should be used in a high-valent pneumococcal conjugate vaccine because use of a single carrier protein may cause an immunological deterioration.

(5) Concerning Difference 4

There is no evidence based on which it should be found that a person skilled in the art could recognize the possibility that 13-valent pneumococcal CRM conjugates will be aggregated by silicone. Based on that, even if a person skilled in the art conceived of a 13-valent pneumococcal CRM conjugate from a 7-valent pneumococcal CRM conjugate, he/she could have never conceived of making it into one that "inhibits aggregation induced by silicone, that is, applying a means for inhibiting aggregation by silicone in addition to changing 7-valent to 13-valent, when manufacturing a vaccine formulation of said 13-valent pneumococcal CRM conjugates.

Incidentally, a publicly known document includes a statement citing existence of silicone oil as one of the factors that accelerate the precipitation of immunoglobulin.

However, immunoglobulin and pneumococcal CRM conjugate are totally different materials though they have a commonality in that they have a protein portion. Therefore, it cannot be said that a person skilled in the art can recognize, based on said statement, that precipitation (aggregation) of 13-valent pneumococcal CRM conjugates is accelerated by silicone oil.

(6) Concerning the effect of the Invention

In the Invention, aluminum phosphate salt and pH buffered salt solution with a pKa of from about 3.5 to 7.5 are mixed into a formulation containing 13-valent pneumococcal CRM conjugates, thereby producing the effect of inhibiting precipitation in said formulation even when the formulation is put in a siliconized container.

Such effect cannot be predicted from Publicly Known Invention 1, which suggests nothing about the silicon-induced aggregation of pneumococcal conjugates, and none of publicly known documents include any statement about the influence of silicone on pneumococcal conjugates or means for solving it. Therefore, it was also difficult to predict the effect of the Invention from those publicly known documents.

(7) Summary

Based on the above, without the need to examine Differences 2 and 3, the Invention is not an invention that a person skilled in the art could have easily made based on Publicly Known Invention 1.

(8) Concerning Difference 3 (supplement)

The Plaintiff alleges that Difference 3 does not exist because the container (syringe or vial stopper) of Publicly Known Invention 1 had been siliconized or at least a person skilled in the art understood as such.

However, there is no sufficient evidence to recognize that the container of Publicly Known Invention 1 had been siliconized. According to publicly known documents, it is possible to understand that syringes and vial stoppers were often siliconized for lubrication, but they do not contain any statement to the effect that syringes and vial stoppers are necessarily siliconized. As there were methods of lubrication other than silicone treatment, it is not the case that persons skilled in the art would get an understanding as alleged by the Plaintiff.

Therefore, the aforementioned allegation of the Plaintiff is not acceptable.

(omitted)

No. 4 Judgment of this court

1. Concerning Ground for Rescission 1 (error in the finding of Difference 3)

The Plaintiff alleges that the Trial Decision contains an error in having found Difference 3. However, the Trial Decision concluded that the Invention involves an inventive step on the grounds that a person skilled in the art could not have easily conceived of Differences 1 and 4. On the other hand, regarding Difference 3, the Trial Decision only found its existence as obiter dictum but did not make a determination concerning whether a person skilled in the art could have easily conceived of the difference. Therefore, this difference has nothing to do with the conclusion of the Trial Decision.

Based on the above, the propriety of having found Difference 3 does not affect the conclusion of the Trial Decision. Therefore, there is no need to make a determination concerning Ground for Rescission 1.

2. Concerning Ground for Rescission 2 (error in the determination concerning Difference 1)

(1) Publicly known documents discussing the development of a pneumococcal vaccine (Exhibit Ko 5-2, etc.) state that the study of a 13-valent pneumococcal conjugate vaccine was being conducted at the time of the Priority Date. In addition, other publicly known documents (Exhibits Ko 7 and 8) state that an 11-valent pneumococcal conjugate vaccine that adopts CRM as carrier protein has been under development.

A 13-valent pneumococcal conjugate vaccine is formulated by adding serotypes 6A and 19A to an 11-valent pneumococcal conjugate vaccine. There are no such special circumstances, such as the fact that the structures and nature, etc. of those serotypes differ from those of 11 types of serotypes contained in 11 or less-valent pneumococcal conjugate vaccines. Therefore, it can be said that a person skilled in the art did not have much difficulty in developing a 13-valent pneumococcal conjugate vaccine while adopting CRM as carrier protein in the same manner as in the case of an 11-valent pneumococcal conjugate vaccine.

(2) Concerning the Defendant's allegation (circumstances that provide the basis for non-easiness of conceiving of Difference 1)

A. Circumstances surrounding the development of 11-valent and 13-valent vaccines

The Defendant alleges as follows: Exhibit Ko 5-2, etc. state only the research and development and clinical trials of a 13-valent pneumococcal conjugate vaccine; in addition, Exhibits Ko 7 and 8 only state that an 11-valent vaccine is at the "preclinical" stage, and it thus cannot be said that the technical idea of a vaccine is disclosed in those documents; therefore, a person skilled in the art cannot conceive of the structure of the Invention pertaining to Difference 1 based on these documents.

However, the Invention relates to formulations that enhance the stability of

immunogenic compositions and inhibits their precipitation ([0007] of the Description). Examination for formulation concerning stability, etc. necessary for providing such medicinal formulation can be conducted separately from the examination of effectiveness as a medicine, including clinical trials. Therefore, even if 11- and 13-valent pneumococcal conjugate vaccines themselves are still under research or at the clinical trial stage, persons skilled in the art are not precluded from conceiving of making them subject to examination, etc. for formulation.

Therefore, the Defendant's allegation is not acceptable.

B. Concerning the choice of carrier protein

The Defendant alleges as follows: even if the number of valences is increased from seven due to concerns about immune response suppression caused by immune interference, it is not reasonable to solely use CRM; it is rather preferable to use multiple carrier proteins to avoid immune interference (Exhibit Ko 48 and Exhibits Otsu 24 and 25). Moreover, the Defendant alleges that there are grounds that inhibit a person skilled in the art from conceiving of the structure of the Invention pertaining to Difference 1 from Publicly Known Invention 1 by citing the following points: it is common general technical knowledge that it is not preferable in terms of immune interference to use CRM as a single carrier protein (Exhibits Otsu 28 and 29), and based on that common general technical knowledge, pharmaceutical companies and researchers were carrying forward the development of a pneumococcal conjugate vaccine using multiple carrier proteins (Exhibit Ko 36, etc.); there was also knowledge that tetanus toxin (TT) is more preferable as carrier protein than CRM in terms of thermal stability (Exhibit Ko 71).

However, whether immune response is deteriorated by immune interference and the degree of the deterioration depend on the type of polysaccharide used as antigen, the number of valences of relevant conjugate vaccine, concentration of each conjugate in the formulation, etc. Therefore, even if a single carrier protein is used in a formulation containing 13-valent pneumococcal CRM conjugates, whether or not it causes immune deterioration and the degree of the deterioration cannot be predicted from the data of other conjugates. In addition, even if immune deterioration is caused by immune interference, it sometimes does not become a serious problem from a clinical perspective (Exhibit Ko 85). Therefore, it cannot be immediately said based on the possibility of immune deterioration caused by immune interference that it is not reasonable to use 13-valent pneumococcal CRM conjugates. In addition, examination in the formulation of a vaccine can be conducted separately from the examination of effectiveness. The fact that immune deterioration may be caused by immune interference and the fact that another carrier protein that is considered preferable from a certain perspective is known are nothing more

than elements to be considered at the level of the effectiveness of a formulation. Therefore, it cannot be said that existence of these facts precludes persons skilled in the art from adopting 13-valent pneumococcal CRM conjugates at the level of formulation.

Therefore, the Defendant's allegation is not acceptable.

(3) Summary

For the reasons described above, it can be said that it was easy for a person skilled in the art to conceive of the structure of Difference 1 of the Invention by adding 6 types of pneumococcal CRM conjugates to Publicly Known Invention 1 to formulate a 13-valent pneumococcal conjugate vaccine. Therefore, the determination of the Trial Decision to the effect that a person skilled in the art could not have easily conceived of Difference 1 is not reasonable.

3. Concerning Ground for Rescission 3 (error in the determination concerning Difference 4)

(1) Concerning the statements in the Description regarding the structure of the matter required to identify the invention of Difference 4

A. The Description contains neither definition nor statement of the specific explanation of "inhibiting the silicon-induced aggregation of polysaccharide-protein conjugates." Therefore, relevant statements in the Description are examined.

B. Concerning the problem to be solved by the invention and means for solving the problem

The Description contains statements that disclose the following content.

(A) (Technical field)

The Invention relates to novel formulations which inhibit precipitation of immunogenic compositions ([0001]).

(B) (Problem to be solved by the invention)

Regarding the stability of immunogenic compositions, many factors, such as carrier protein, conjugate chemistry, the number of conjugate sites, length of polysaccharide chains, pH, storage buffer, storage temperature, and freeze-thaw cycles, must be considered ([0003] and [0004]). In addition, it is known that in an insulin formulation using a siliconized syringe, insulin was aggregated and inactivated due to silicone oil incorporation. However, it is indispensable to siliconize the surface of a syringe for lubricating a rubber stopper in a syringe and preventing protein absorption ([0005] and [0006]).

The Invention is intended to provide formulations which stabilize immunogenic compositions against silicone oil interactions, etc. and inhibit their precipitation ([0007] and [0008]).

(C) (Means for solving the problem)

The formulation of the Invention is a formulation which inhibits the silicon-induced precipitation of polysaccharide-protein conjugates contained in a siliconized container ([0022]).

(D) (Effect of the invention)

By a formulation pertaining to the Invention, it is possible to stabilize an immunogenic composition to be processed, developed, formulated, manufactured, and/or stored and inhibit its microparticle formation (e.g., aggregation, precipitation) in a container ([0051]).

C. Concerning the relationship between aluminum salt and silicon-induced aggregation in 13-valent pneumococcal CRM conjugates (13vPnC)

(A) Matters disclosed in the Description

A 13-valent pneumococcal CRM conjugate immunogenic composition [i] wherein pH buffered salt solution is 5mM succinate buffer (pH 5.8) and [ii] which contains 0.25mg/ml aluminum phosphate as aluminum salt (hereinafter referred to as "Working Example 13vPnC Composition") is stated as one of the embodiments of the Invention ([0022], [0023], [0029], and [0057]). As Working Example 3, an experiment on the production of a microparticle formation (aggregation) in a siliconized syringe was conducted with respect to a formulation comprising Working Example 13vPnC Composition and a formulation obtained by removing aluminum phosphate therefrom ([0117] to [0124]).

Here, 13-valent pneumococcal CRM conjugates contained in Working Example 13vPnC Composition (hereinafter sometimes referred to as "13vPnC") correspond to 13-valent pneumococcal conjugates mentioned in (iii) of the formulation of the Invention. In addition, the Description does not state any other specific formulation that fulfills the structure of the Invention relating to the composition.

According to the result of the experiment, when a composition from which aluminum phosphate was removed was filled into a siliconized container, 13vPnC particles were produced in a readily observable manner while when Working Example 13vPnC Composition containing aluminum phosphate was filled into a siliconized container, production of 13vPnC particles was significantly reduced ([0117]). In addition, in another experiment wherein a composition from which aluminum phosphate was removed was contacted with components (stopper, etc.) of a container, no particles were detected when the composition was contacted with a non-siliconized component while formation of particles was induced when it was contacted with a siliconized component ([0118] to [0124]).

(B) It is possible to understand based on the disclosure of the Description mentioned in

(A) above that the formulation of the Invention has a composition comprising (i) to (iii) and is a formulation wherein the silicon-induced aggregation of pneumococcal conjugates is inhibited through inclusion of aluminum salt mentioned in (ii) in its composition.

D. Concerning the relationship between free 13vPnC and silicon-induced aggregation

(A) Matters disclosed in the Description

Working Example 13vPnC Composition contains about 85% of 13vPnC bound to aluminum phosphate and about 15% of free 13vPnC (not bound to aluminum phosphate) ([0128]). When supernatant obtained by centrifuging Working Example 13vPnC Composition is contacted with a component of a siliconized container, aggregation is formed ([0129]).

On the other hand, in a 7-valent pneumococcal CRM conjugate immunogenic composition (composition obtained by removing six types of serotypes from Working Example 13vPnC Composition; hereinafter referred to as "Comparative Example 7vPnC Composition"), all of the 7-valent pneumococcal CRM conjugates (hereinafter referred to as "7vPnC") are bound to aluminum phosphate, and there is no free 7vPnC ([0128]). Even if supernatant obtained by centrifuging Comparative Example 7vPnC Composition is contacted with a component of a siliconized container, no aggregation is formed ([0129]).

The result of this experiment suggests that existence of free 13vPnC (not bound to aluminum phosphate) played a part in silicon-induced aggregation ([0129]).

(B) The following can be understood based on the disclosure of the Description mentioned in (A) above: in the formulation of the Invention, silicon-induced aggregation is inhibited by having aluminum phosphate contained in a composition (C.(B) above) because a large portion of 13vPnC (85% in the example mentioned in (A) above) is bound to aluminum phosphate, and thereby, the amount of free 13vPnC is remarkably reduced (to 15% in the example mentioned in (A) above).

That is, owing to adoption of a composition comprising (i) to (iii) mentioned above, the formulation of the Invention is in a state where aluminum salt and 13vPnC are bound to each other and the amount of free 13vPnC is reduced to the intended amount. As the effect of such state, silicon-induced aggregation is inhibited.

E. Concerning the relationship between aluminum salt and silicon-induced aggregation in 1-valent pneumococcal CRM conjugates

(A) Matters disclosed in the Description

In an experiment wherein formulations that do not contain aluminum phosphate but contain 1-valent PnC (whose serotype was 6B) at the same concentration (61μg/ml) in lieu of 13vPnC (total concentration of PnC of all serotypes was about 61μg/ml) were

formulated and silicone was added thereto at a concentration of 2ppm to 100ppm, aggregation was formed at all silicone concentrations ([0125] and [0126]).

In addition, an experiment was conducted using 1-valent pneumococcal CRM conjugates (whose serotype was 4 or 6B) to examine whether aggregation is formed when formulations containing aluminum phosphate and formulations not containing it are contacted with a component of a siliconized container. As a result, aggregation was formed in formulations not containing aluminum phosphate even if protein concentration was low, irrespective of whether the serotype is 4 or 6B. On the other hand, aggregation was formed in formulations containing aluminum phosphate only when protein concentration was higher than a certain level. In addition, formulations using serotype 4 and those using serotype 6B differ in bindingness to aluminum, and the concentration at which aggregation began to be formed when protein concentration in formulations containing aluminum phosphate was increased differed between formulations using serotype 4 and those using serotype 6B ([0130] and [0131]).

(B) The following can be understood based on the disclosure of the Description mentioned in (A) above: silicon-induced aggregation is formed in formulations to which aluminum salt is not added if the concentration of pneumococcal CRM conjugates (protein concentration) is increased, even if the number of valences of the formulations is one.

That is, in the Invention, inhibition of silicon-induced aggregation through inclusion of aluminum salt (C.(B) above) is not an effect peculiar to 13-valent pneumococcal CRM conjugates but is an effect obtained irrespective of the number of valences of pneumococcal CRM conjugates. The degree of that effect is determined by the relative relationship between the amount of pneumococcal conjugates in a formulation and the amount of aluminum phosphate therein. In addition, the degree of said effect also differs depending of the serotype of pneumococcal CRM conjugates.

F. Concerning the relationship between pH-adjusted buffer solution and silicon-induced aggregation

The Description neither states the influence of pH buffer salt solution on silicon-induced aggregation and binding between aluminum salt and pneumococcal CRM conjugates, etc. nor discloses a 13vPnC immunogenic composition using pH buffer salt solution that is different from 5mM succinate buffer. Therefore, the way pH buffer salt solution mentioned in (i) in the composition identified by the Invention is related to the effect of inhibiting silicon-induced aggregation cannot be understood based on the disclosure of the Description.

However, the Description discloses that the ratio of aluminum phosphate-binding

protein to all proteins changes if different pH buffer salt solutions are used in an experiment for examining bindingness between protein and aluminum phosphate in a formulation that uses a protein in lieu of 13vPnC of the Invention and also contains surfactant ([0144] to [0146]). Therefore, it can be presumably recognized that in the formulation of the Invention, pH buffer salt solution mentioned in (i) can also affect bindingness between aluminum salt mentioned in (ii) and pneumococcal CRM conjugates mentioned in (iii).

(2) Concerning the technical significance of the matter required to identify the invention pertaining to Difference 4

In light of the matters disclosed in the Description mentioned in (1) above, the technical significance of the matter required to identify the invention, i.e., that the formulation of the Invention produces the effect of inhibiting silicon-induced aggregation, is understood as follows.

[i] Free pneumococcal conjugates play a part in silicon-induced aggregation, irrespective of the serotype of pneumococcal bacteria.

[ii] The formulation of the Invention has a composition comprising (i) to (iii), and as a result, in a solution, pneumococcal CRM conjugates and aluminum salt are bound to each other and the amount of free pneumococcal CRM conjugates is relatively reduced.

[iii] As a result of being in the state mentioned in [ii] above, silicon-induced aggregation based on the principle mentioned in [i] above is inhibited.

(3) Technical significance of Publicly Known Invention 1

Publicly Known Invention 1 is found from 7-valent Prevenar. Taking into account that 7-valent Prevenar is a medicine that has been made available in the market, it is considered permissible to refer to documents on product information about 7-valent Prevenar, etc. when intending to understand the technical significance of Publicly Known Invention 1.

Attachment B of Exhibit Ko 1 is the European Public Assessment Report (EPAR) for 7-valent Prevenar issued by the European Agency for the Evaluation of Medical Products (EMEA). According to the text of Exhibit Ko 1 (an affidavit concerning the result of search of internet archive), it is a publication that became available to the public prior to the Priority Date.

In addition to the composition of Publicly Known Invention 1, the same report states that seven types of pneumococcal bacteria are "conjugated to CRM_{197} carrier protein and absorbed on aluminum phosphate (0.5mg)." However, the same report contains no statement that discloses or suggests the technical significance of the fact that 7-valent pneumococcal CRM conjugates are absorbed on aluminum phosphate, and no statement

concerning said technical significance can be found even through careful examination of other documents in the evidence on this case.

(4) Whether a person skilled in the art could have easily conceived of Difference 4

As mentioned in (2) above, the matter required to identify the Invention pertaining to Difference 4, that is, "inhibiting the silicone-induced aggregation of polysaccharide-protein conjugates contained in a siliconized container," means that silicon-induced aggregation in which free pneumococcal CRM conjugates play a part is inhibited because of being in the condition in which pneumococcal CRM conjugates and aluminum salt are bound to each other and the amount of free pneumococcal CRM conjugates in the solution is reduced to the intended amount.

On the other hand, according to (3) above, it can be said that when seeing Publicly Known Invention 1, a person skilled in the art only recognizes that pneumococcal CRM conjugates absorbed on aluminum phosphate are contained in the formulation of Publicly Known Invention 1 and that it was not easy for a person skilled in the art to recognize whether free pneumococcal conjugates exist in the solution of the formulation of Publicly Known Invention 1 and the amount thereof in relation to the problem of silicone aggregation in which free pneumococcal conjugates play a part. In addition, the amount of free pneumococcal CRM conjugates in the formulation of the Invention can differ depending on the amount of pneumococcal CRM conjugates having six types of serotypes added to 7vPnC of Publicly Known Invention 1 and also differs depending on the absorbability on aluminum salt of each of the serotypes added. Therefore, a person skilled in the art cannot even predict whether free pneumococcal CRM conjugates exist in the solution of a formulation having the composition of the Invention based on Publicly Known Invention 1. As a result, a person skilled in the art also cannot predict whether silicon-induced aggregation in which free pneumococcal CRM conjugates play a part is inhibited by a formulation having the composition of the Invention.

For the reasons described above, based on Publicly Known Invention 1, a person skilled in the art could not have easily conceived of the matter required to identify the invention pertaining to Difference 4, that is, the point that a formulation has a composition comprising (i) to (iii) in order to inhibit the silicon-induced aggregation of pneumococcal CRM conjugates in a siliconized container.

(5) Concerning the Plaintiff's allegations

A. Concerning the allegation that Difference 4 is not a substantial difference

The Plaintiff alleges as follows: Difference 4 is substantially a common feature and is not a difference, taking into account that when seeing product information about 7-valent Prevenar, a person skilled in the art understood that silicon-induced aggregation is

also inhibited in 7-valent Prevenar for some reason and that inhibition of silicon-induced aggregation by aluminum phosphate that occurred in 7-valent Prevenar also naturally occurs in 13vPnC, putting aside the degree of inhibition.

However, the statement, "(t)he vaccine should … be inspected visually for any particulate matter and/or variation of physical aspect prior to administration," in product information about 7-valent Prevenar (Attachment B of Exhibit Ko 1) can also be understood as an instruction to confirm whether the vaccine has not changed in quality due to a defect in manufacturing or storage as a general precaution for the use of a medicine for injection. Therefore, it cannot be necessarily said that, when seeing said statement, a person skilled in the art at the time of the Priority Date, when there was no knowledge about the silicon aggregation of polysaccharide-protein conjugates, could understand that aggregation can be formed but is ordinarily inhibited, as alleged by the Plaintiff. Furthermore, it must be said that it is difficult for such person skilled in the art to determine whether such aggregation is induced by silicone. On the other hand, the Invention clearly identifies the cause of aggregation of 13vPnC as induction by silicone and then states inhibition of such aggregation as a matter required to identify the invention. Therefore, in this regard, the Invention can be considered to be different from Publicly Known Invention 1.

Consequently, the Trial Decision contains no error in having found Difference 4, and the aforementioned allegation of the Plaintiff is not acceptable.

B. Concerning the easiness of discovering the problem, that is, inhibition of silicon-induced aggregation

The Plaintiff alleges as follows: silicon-induced aggregation in protein formulations had been known, and persons skilled in the art had understood that protein aggregation is the driving force for polysaccharide-protein conjugate aggregation; therefore, persons skilled in the art could predict that silicon-induced aggregation is formed in a 13-valent pneumococcal CRM conjugate formulation in which the protein content is increased by adding six types of pneumococcal CRM conjugates to Publicly Known Invention 1.

However, publicly known documents used by the Plaintiff as grounds for its allegation (Exhibits Ko 25, 26, and 71) only contain statements about aggregation associated with the structural instability of polysaccharide-protein conjugates for which carrier protein is CRM or tetanus toxin (TT). Therefore, it cannot be said that silicon-induced aggregation of polysaccharide-protein conjugates had been recognized by persons skilled in the art as a problem at the time of the Priority Date based on these publicly known documents.

Therefore, the aforementioned allegation of the Plaintiff is not acceptable.

C. Concerning the easiness of applying the means for solving the problem

As mentioned in B. above, a person skilled in the art could not recognize the problem to be solved by the Invention. Therefore, in this regard, a person skilled in the art could not have easily conceived of the Invention. However, for confirmation, this Court also examines the Plaintiff's allegation concerning whether a person skilled in the art could have easily conceived of application of the means for solving the problem.

(A) Concerning knowledge about means for solving the silicon-induced aggregation of protein formulations

The Plaintiff alleges that a person skilled in the art could adopt knowledge about means for solving silicon-induced aggregation in protein formulations in order to solve said problem.

However, publicly known documents used by the Plaintiff as grounds for its allegation (Exhibits Ko 3 and 69) contain statements about the silicon-induced aggregation of a protein medicine but not about anything concerning silicon-induced aggregation of polysaccharide-protein conjugates. On the other hand, it had been known that the structural instability and aggregation of polysaccharide-protein conjugates are affected not only by the protein portion but also by the polysaccharide portion (Exhibits Ko 25 and 50). As protein and polysaccharide differ in structure and nature, it is naturally expected that they behave differently. On that basis, knowledge about the silicon-induced aggregation of a protein medicine stated in the aforementioned publicly known documents (Exhibits Ko 3 and 69) is not found to be immediately applicable to the silicon-induced aggregation of polysaccharide-protein conjugates. In addition, the aforementioned publicly known documents only disclose addition of surfactant and reduction of the silicone content, respectively, as a means for solving the problem of silicon-induced aggregation of a protein medicine, and do not mention addition of aluminum salt, which is a structure of the Invention. Therefore, a person skilled in the art would not have conceived of the structure of the Invention even by applying the knowledge stated in the aforementioned publicly known documents concerning means for solving the silicon-induced aggregation of a protein formulation to Publicly Known Invention 1.

Therefore, the aforementioned allegation of the Plaintiff is not acceptable.

(B) Concerning knowledge about an effect produced by aluminum salt

The Plaintiff alleges that a person skilled in the art understood that the aggregation of a vaccine by silicone that presents a hydrophobic interface can be prevented by using aluminum salt as adjuvant because he/she had knowledge that the absorption of protein on a hydrophobic surface in association with the occurrence of an aggregate can be prevented by aluminum particles (Exhibits Ko 81-3 and 76).

However, in the aforementioned knowledge, absorption of protein on the hydrophobic surface of a container was understood as being associated with interaction between the surface of the container and protein molecules at the interface between a liquid (formulation) and a solid (container) (Exhibit Ko 81-3). On the other hand, the silicon-induced aggregation of a protein medicine is considered to be associated with existence of a tiny amount of silicone and protein denaturation at the air-liquid interface (Exhibit Ko 3) and influence of silicone on intermolecular interaction that plays a part in protein bond (Exhibit Ko 69). It is thus not recognized that silicon-induced aggregation was considered to occur due to absorption of protein on silicone. Therefore, it can be said that it was difficult for a person skilled in the art to immediately apply the aforementioned knowledge that absorption of protein on a hydrophobic surface is inhibited by aluminum particles to the inhibition of silicon-induced aggregation of pneumococcal CRM conjugates.

Therefore, the aforementioned allegation of the Plaintiff is not acceptable.

D. Concerning an alternative allegation that the matter required to identify the invention pertaining to Difference 4 is nothing more than a mere "discovery"

The Plaintiff alleges as follows: the matter required to identify the invention pertaining to Difference 4 is nothing more than the "discovery" of a mechanism that also occurred in Publicly Known Invention 1 (7-valent Prevenar), wherein when the well-known conventional art of choosing aluminum salt as adjuvant for a vaccine formulation is adopted, aluminum salt shows the effect of inhibiting silicon aggregation in a pneumococcal CRM conjugate vaccine formulation; therefore, it is unjust to find involvement of an inventive step in the Invention on the basis of Difference 4 because it would result in granting an exclusive right to free art.

However, this allegation can be considered to be the same in terms of essence as the aforementioned allegation that the Invention and Publicly Known Invention 1 are substantially identical with each other (that is, the argument that the uniqueness of the Invention exists merely in the "discovery" of a mechanism of aggregation can be established only on the premise that the Invention and Publicly Known Invention 1 are substantially identical with each other and have no difference in the structure of the invention). This allegation is not acceptable, as already explained above.

Therefore, the aforementioned alternative allegation of the Plaintiff is not acceptable.

4. Concerning Ground for Rescission 4 (error in the determination concerning the effect of the Invention)

As Difference 4 itself is a matter required to identify the invention in relation to the effect of the Invention, it can be said that there was no need to further examine the

prominence of the working-effect of the Invention as long as there is no error in the determination of the Trial Decision that a person skilled in the art could not have easily conceived of Difference 4, as mentioned in 3. above. Therefore, the propriety of the determination of the Trial Decision concerning the prominent working-effect of the Invention does not affect the propriety of the conclusion of the Trial Decision and thus does not need to be examined.

5. Conclusion

For the reasons described above, the conclusion of the Trial Decision contains no error. Therefore, the Plaintiff's claim should be dismissed.

Intellectual Property High Court, Third Division
Presiding judge: TSURUOKA Toshihiko
Judge: UEDA Takuya
Judge: TSUNO Michinori

Attachment

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End