Appeal decision

Appeal No. 2013-22460

Germany
Appellant NOVARTIS VACCINES & DIAGNOSTICS GMBH & CO KG

Osaka, Japan
Patent Attorney YAMAMOTO, Shusaku

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Conclusion
The appeal of the case was groundless.

Reason
1. History of the procedures
   The present application is a divisional application filed on November 8, 2011 from Patent Application No.2011-158471 filed on July 19, 2011, which is a divisional application from Patent Application No.2007-530801 filed on September 9, 2005 as an international filing date (priority claim under the Paris Convention: September 9, 2004, European Patent Office(EP)). Decision of refusal was issued on July 12, 2013. For this, an appeal against the examiner's decision of refusal was requested, and a written amendment was submitted on November 18, 2013.

2. The Invention
The inventions according to Claims 1 to 8 of the present application are
specified by the matters described in Claims 1 to 8 of the November 18, 2013 written amendment. The invention according to Claim 1 above (hereinafter referred to as The "Invention") is as follows.

"[Claim 1]
A process for preparing a vaccine antigen in a culture of a Vero cell line, comprising a step in which porcine circovirus is tested"

3. Matters described in Cited Document
(1) Publication distributed before the priority date which was cited in reasons for refusal of the examiner's decision, LEVANDOWSKI R A, DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, 1999, V98, P171-175, 197 (hereinafter referred to as the "Cited Document 1"), describes the following matters.
(A) "Regulatory perspective in the United States on cell cultures for production of inactivated influenza virus vaccines" (Title in page 171)

(B) "Abstract: The United States Code of Federal Regulations requires that all influenza virus vaccines produced for use in the United States adhere to specific regulatory standards, including the demonstration of safety and efficacy. For vaccines produced in cell lines, rigorous characterization for manufacturing is particularly important. Influenza vaccines produced by the passage of viruses in mammalian cell lines will require careful evaluation to ensure the removal or inactivation of potential adventitious agents." (Abstract in page 171)

(C) "The characterization of cells used for manufacturing is outlined in 21CFR610.18. ... According to 21CFR610.18(c), the characterization of a cell line shall include .... In addition, information on...
(iii) testing the cell line for potential microbial agents associated with the cell line must be developed. In particular, there is great concern for the potential for cell lines to support or contain known or suspected human pathogens." (lines 12 to 22 of page 173)

(D) "The use of mammalian tissue cultures raises somewhat different questions relating to safety. One concern is that influenza virus vaccines produced in mammalian cell cultures could harbour agents similar to human pathogens which might be less likely to replicate in eggs. ... Some of the viruses capable of replication in cell lines currently being considered for use in manufacturing influenza virus vaccines are shown in Table 2 (see addendum). ..."
Table 2: Virus replication in Vero and MCDK

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Virus replication reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vero</td>
<td>Alphavirus, arenavirus, bunyavirus, flavivirus, poliovirus, reovirus, rubellavirus, rubeola, simian adenovirus, SV-5, SV-40</td>
</tr>
<tr>
<td>MCDK</td>
<td>...</td>
</tr>
</tbody>
</table>

" (from the fifth line from the bottom of page 173 to line 4 of page 174, and, the latter paragraph of page 174)

Publication distributed before the priority date which was cited in reasons for refusal of the examiner's decision, Veterinary Immunology and Immunopathology, 1994, vol. 43, no 4, p.357-371 (hereinafter referred to as the "Cited Document 2"), describes the following matters.

(E) "Production, preliminary characterization, and applications of monoclonal antibodies to porcine circovirus" (Title in page 357)

(F) "Abstract

The preparation of monoclonal antibodies (mAbs) to porcine circovirus is described. Preliminary characterization was ... included indirect immunofluorescence staining patterns obtained following immunostaining of both a porcine circovirus (PCV)-persistently infected pig kidney (PK/15/W) and Vero (Vero-PCV) cell line."

(G) "2.1. Virus

A PCV-persistently infected continuous pig kidney cell line (PK/15/W) was used to prepare a pool of virus. ... Endpoints were read by indirect immunofluorescence (IIF). (from the 15th line from the bottom of page 358 to line 1 of page 359)

(H) "2.5.3. IIF staining pattern

Acetone-fixed cultures of PK/15/W cells, PK/15/H cells, and PCV-persistently infected Vero cells (Vero-PCV) were immunostained ... .

A persistently infected Vero cell line was obtained following inoculation of Vero with PCV. ... cultures of Vero cells, growing in ... flasks, were inoculated with ... the PCV pool. This inoculum was allowed to absorb to the cells ... before ...incubation .... Following this incubation, ... the cells subcultured for a further 3 days before being subcultured again. This was repeated indefinitely with cell stocks being stored at selected passage levels in liquid nitrogen. Coverslip preparations were prepared following the primary inoculation, and after six, 15, and 25 subcultures.
These preparations, and cultures of PK/15/W and PK/15/H were immunostained for PCV antigen by IIF using the polyclonal rabbit anti-PCV antiserum and selected mAbs." (lines 1 to 15 of page 361)

(I) "Following inoculation of Vero with PCV, IIF staining using rabbit PCV antibody revealed large numbers of cells with discrete cytoplasmic staining and occasional cells exhibiting intensely stained cytoplasmic inclusions. No nuclear staining was observed at this time; however, nuclear staining was observed in a few cells by the sixth subculture of this PCV-infected cell line (Vero-PCV). Immunostaining patterns observed following incubation of cells from the 15th and 25th subcultures of the Vero-PCV with rabbit serum were identical with those observed following immunostaining of PK/15/W cultures, with all cells showing discrete pin-like staining in the cytoplasm and a few cells exhibiting both dense nuclear and cytoplasmic staining. A few cells were seen containing large intracytoplasmic inclusions which immunostained intensely (FIG. 1(a))." (lines 9 to 19 of page 366)

(2) According to the described matter (A) of Cited Document 1, Cited Document 1 is a document relating to a method for cell cultures for production of inactivated influenza virus vaccines in the United States. According to the described matter (B), it is described that influenza vaccines produced by the passage of viruses in mammalian cell lines will require careful evaluation to ensure the removal or inactivation of potential adventitious agents. According to the described matter (C), it is described that, relating to the characterization of cells, information for testing the cell line for potential microbes associated with the cell line must be developed, and there is great concern for the potential for cell lines to support or contain known or suspected human pathogens. According to the described matter (D), Vero cell lines are cell lines currently being considered for use in manufacturing influenza virus vaccines, and some of the viruses capable of replication in the cells are listed.

Summing up these descriptions in Cited Document 1, it is found that the following invention (hereinafter referred to as the "Cited Invention") is described in Cited Document 1.

"A method for production of an influenza vaccine by subculture of a virus in a Vero cell line,
comprising a step in which the Vero cell line is tested, for a potential microbe associated with the Vero cell."
4. Comparison

Comparing the Invention with the Cited Invention, "a method for production of an influenza vaccine by subculture of virus in a Vero cell line" of the Cited Invention corresponds to "a process for preparing a vaccine antigen in a culture of a Vero cell line" of the Invention. Further, "comprising a step in which the Vero cell line is tested, for a potential microbe associated with the Vero cell" of the Cited Invention and "comprising a step in which porcine circovirus is tested" of the Invention are not different in comprising a step in which a potential microbe associated with the Vero cell line is tested.

Therefore, the two inventions coincide on

"A process for preparing a vaccine antigen in a culture of a Vero cell line, comprising a step in which a potential microbe associated with the Vero cell line is tested."

and are different in the following point.

- In the Invention, "porcine circovirus" is adopted as "a potential microbe associated with the Vero cell line" (hereinafter referred to as the "different feature").

5. Judgment

The different feature will be examined as follows.

According to the described matter (C) of Cited Document 1, it is described in Cited Document 1 that there is great concern for the potential for cell lines to support or contain known or suspected human pathogens. According to the described matter (D), it is described that some of the viruses capable of replication in Vero cell lines are shown in Table 2. In that case, it is obvious that a person skilled in the art coming into contact with these descriptions has concern in any virus including some of the above viruses.

On the other hand, according to the described matter (E) of Cited Document 2, Cited Document 2 is a document relating to monoclonal antibodies against porcine circovirus. According to the described matter (F), it is described that Vero (Vero-PCV) cell lines persistently infected with porcine circovirus (PCV) were used in preliminary characterization of the monoclonal antibodies. According to the described matter (H), it is described that a persistently infected Vero cell line was obtained following inoculation of Vero with PCV, and the coverslip preparations were prepared following the primary inoculation, and after 6, 15, and 25 subcultures. According to the described matter (I), IIF staining using rabbit PCV antibody revealed large numbers of cells with cytoplasmic staining in Vero after first inoculation, nuclear staining was
observed in a few cells after the sixth subculture, and all cells were stained in the cytoplasm and a few cells exhibited both dense nuclear and cytoplasmic staining, identical to those observed following immunostaining of PK/15/W cultures, after the 15th and 25th inoculation. According to the described matter (G), it is described that PK/15/W was used to prepare a pool of virus persistently infected with PCV. In that case, it is obvious for a person skilled in the art coming into contact with these descriptions that Vero cells were infected with PCV and persistently infected after 6, 15, 25 subcultures; and the region immunostained by rabbit PCV antibody was spread from cytoplasm into nucleus with the subcultures, identical with those observed following immunostaining of PK/15/W cultures used to prepare a pool of virus, and thus PCV is replicated in Vero.

Therefore, it is not difficult for a person ordinarily skilled in the art coming into contact with these Cited Documents 1 and 2 to pay attention to porcine circovirus as "potential microbes associated with the Vero cell line" in the Cited Invention.

Further, even considering the description of the invention, the Invention does not have excellent effect that a person ordinarily skilled in the art cannot predict from the descriptions in Cited Documents 1 and 2.

The appellant submitted Evidence A No. 1 in the written opinion for the examiner's decision, and alleges that "... in Evidence A No. 1, it is stated that, in spite of the presence of virus protein, Vero cells infected with PCV did not produce infectious virus particles and the Vero cells did not support replication of PCV (Evidence A No. 1 page 290). It is thought that a person skilled in the art knowing of Cited Document 2 (Note for the body: the same as Cited Document 2) also knows of Evidence A No. 1. A person ordinarily skilled in the art coming into contact with these documents understands that some of the PCV proteins are expressed in Vero cells infected with PCV; however, infectious PCV cannot be replicated in the Vero cells.

As described above, in manufacturing vaccines, only a pathogen causing risk to a patient being administered vaccines manufactured is a problem during manufacturing of virus. Since it was thought that Vero cells could not support the replication of infectious PCV, a person skilled in the art did not think that PCV has a problem in manufacturing virus vaccines in Vero cells. Therefore, at the time of preparing vaccine antigens, there was no motivation to test PCV."
However, as instructed above, it is obvious for a person ordinarily skilled in the art that Cited Document 2 shows that PCV was replicated in Vero. The description of Evidence A No. 1, indicated by the appellant, that Vero cells do not support the replication of PCV is based on the experiment using specific plasmid which is different from the experiment in Cited Document 2, and does not deny the experiment in Cited Document 2. Thus, though Evidence A No. 1 was known to a person skilled in the art, it is not found that a person skilled in the art thought Vero cells could not support the replication of infectious PCV. Further, there is no doubt for a person skilled in the art coming into contact with Cited Document 2 and Evidence A No. 1 that Vero cells were infected with PCV; that is, it is possible that PCV is associated with Vero cells or Vero cells include PCV. As instructed above, it is described in Cited Document 1 that in characterization of cell lines, testing the cell line for potential microbes associated with the cell line must be developed and there is great concern for the potential for cell lines to support or contain known or suspected human pathogens, and it is found that a person skilled in the art has already arrived to the Invention from the Cited Invention at the time when a person skilled in the art knew, by Cited Document 2, that Vero cells were infected with PCV.

Therefore, the above appellant's allegation cannot be accepted.

6. Conclusion

As described above, since the Invention would have been easily made by a person ordinarily skilled in the art based on the inventions described in Cited Documents 1 and 2, the appellant should not be granted a patent for the Invention under the provisions of Article 29(2) of the Patent Act.

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

March 31, 2015

Chief administrative judge: NAITO, Shinichi
Administrative judge: OKUBO, Motohiro
Administrative judge: OTAKU, Ikuji