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D E C I S I O N
of 14 September 2004

Case Number: T 1127/02 - 3.3.4

Application Number: 93307185.4

Publication Number: 0588578

IPC: A61K 39/00

Language of the proceedings: EN

Title of invention:

Composition containing both a soluble and an insoluble form of an immunogen

Patentee:

CONNAUGHT LABORATORIES INCORPORATED

Opponent:

GlaxoSmithKline Biologicals s.a.

Headword:

Soluble and insoluble form of an antigen/CONNAUGHT

Relevant legal provisions:

EPC Art. 54, 56, 83

Keyword:

"Main request - novelty (no)"

"Auxiliary request - sufficiency of disclosure, novelty, inventive step (yes)"

Decisions cited:

T 0256/87, T 0241/89, T 0612/92, T 0694/92, T 0396/99

Catchword:

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Case Number: T 1127/02 - 3.3.4

DECISION
of the Technical Board of Appeal 3.3.4
of 14 September 2004

Appellant: GlaxoSmithKline Biologicals s.a.
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
20 August 2002 concerning maintenance of
European patent No. 0588578 in amended form.

Composition of the Board:

Chairwoman: U. Kinkeldey
Members: M. Wieser
S. Hoffmann

Summary of Facts and Submissions

I. The appeal was lodged by the Opponents (Appellants) against the decision of the Opposition Division, whereby the European patent No. 0 588 578 was maintained in amended form pursuant to Article 102(3) EPC.

II. The Opposition Division had decided that claims 1 to 7 of the third auxiliary request before them met the requirements of the EPC.

Claim 1 thereof read:

"A composition for eliciting an immune response to an antigen in an animal, comprising a first physio-chemical form of said antigen favouring presentation of the antigen by B cells to T cells in the animal, and a second physio-chemical form of said antigen favouring presentation of the antigen by accessory cells to T cells in the animal, characterized in that said first physio-chemical form is a soluble form of said antigen and said second physio-chemical form is an insoluble form of said antigen."

III. The Board expressed their preliminary opinion in a communication dated 19 March 2004.

Oral proceedings were held on 14 September 2004.

IV. At the oral proceedings the Patent Proprietors (Respondents) filed an auxiliary request consisting of claims 1 to 4. Claim 1 thereof read:

"A composition for eliciting an immune response to an antigen in an animal, comprising a first physio-chemical form of said antigen favouring presentation of the antigen by B cells to T cells in the animal, and a second physio-chemical form of said antigen favouring presentation of the antigen by accessory cells to T cells in the animal, characterized in that said first physio-chemical form is a soluble form of said antigen and said second physio-chemical form is an insoluble form of said antigen and characterised in that one physio-chemical form of antigen is lipidated and the other physio-chemical form is not lipidated."

- V. The Appellants requested that the decision under appeal be set aside and that the patent be revoked.

The Respondents requested that the appeal be dismissed and the patent be maintained on the basis of the main request (claims 1 to 7 as maintained by the Opposition Division), or on the basis of claims 1 to 4 of the auxiliary request filed during oral proceedings.

- VI. The following documents are referred to in this decision:

(12) WO-A-91/14 449

(13) Acad. Press Dictionary of Science and Technology;
<http://www.harcourt.com.dictionaty/def/9/5/3/9553000.html>

(20) J.Immunol., vol. 119, no. 6, 1977, p. 2073 to 2077

(21) Virology, vol. 69, 1976, p. 511 to 522

VII. The submissions by the Appellants as far as they are relevant to the present decision may be summarised as follows:

The two physio-chemical forms of an antigen were defined in claim 1 of the main request, firstly by favouring different paths of presentation of the antigen to T cells, and secondly by the feature that one form was soluble while the other form was insoluble. The first definition was based on a theory to which the Patentees did not wish to be bound. The patent contained no information how to determine the way of presentation of the antigen to T cells. To develop a method for this determination would resume to undue burden. Moreover, the patent lacked any definition of the terms "soluble" and "insoluble" used in the characterising part of claim 1 of the main request. The skilled person working in the field of vaccines would not know when he was working within the area defined by the scope of this claim. Consequently, contrary to the requirements of Article 83 EPC, the patent did not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

The subject matter of claim 1 of the main request was anticipated (Article 54 EPC) at least by the disclosure in documents (12), (20) and (21), which all disclosed a composition containing a soluble and an insoluble form of an antigen.

The claims of the auxiliary request were not acceptable for formal reasons, as they contravened the requirements of Articles 123(2) and 84 EPC. They were open to the same objections under Article 83 EPC as the claims of the main request.

Claim 1 of the auxiliary request lacked novelty over document (12) which disclosed compositions containing a lipidated and a not lipidated form of an antigen.

Starting from either document (12) or (20), no technical problem to be solved could be identified by providing a composition according to claim 1 of the auxiliary request, which for this reason lacked an inventive step.

VIII. The submissions by the Respondents as far as they are relevant to the present decision may be summarised as follows:

The requirements of Article 83 EPC were met by the main request. The patent disclosed three examples of pairs of antigens according to claim 1 of the main request.

Methods for determining the way of presentation of an antigen to T cells were known to the skilled person at the relevant date of the patent in suit. As the soluble form of an antigen was always favourably presented by B cells to T cells, while the insoluble form thereof was favourably presented by accessory cells to T cells, these methods could be used by the skilled person to distinguish between the soluble and insoluble form of an antigen.

Moreover, it was evident from the patent that the solubility/insolubility of an antigen related to the situation after administration of the vaccine, i.e. when the antigen encounters the host's immune system.

None of the documents cited by the Appellants disclosed a composition comprising two physio-chemical forms of an antigen according to claim 1 of the main request.

Document (12) did not disclose a composition comprising a soluble, non-lipidated and an insoluble, lipidated form of an antigen, according to claim 1 of the auxiliary request.

The subject-matter of claim 1 of the auxiliary request was not obvious in the light of document (20), representing the closest prior art, either if taken alone or in combination with any other cited prior art document.

Reasons for the Decision

Main Request

Sufficiency of disclosure (Article 83 EPC)

1. In the assessment as to whether a European application fulfils the requirement of Article 83 EPC, it is required according to the case law of the Boards of Appeal that, for the disclosure of an invention to be sufficiently clear and complete, the skilled person, on the basis of the information provided in the application itself and by using the general knowledge,

has to be able to achieve the desired result without undue burden and without exercising any inventive skill (cf decisions T 694/92 OJ EPO 1997, 408 and T 612/92 of 28 February 1996).

2. Claim 1 refers to a composition comprising two physio-chemical forms of an antigen. The claim states in its introductory part that the first form of the antigen favours presentation of said antigen by B cells to T cells in an animal, and the second form favours presentation of said antigen by accessory cells to T cells in an animal. This statement reflects a theoretical explanation, given in the patent to explain the technical effect caused by the claimed composition upon administration to a naive animal, namely the achievement of an enhanced immunogenic response (cf page 2, column 2, lines 2 to 54 of the granted patent).

In the specification of the patent it is stated that the Respondents do not wish to be bound to this theory, which, moreover, is not substantiated by any data. In this situation the Board cannot regard this as being a technically characterizing feature of the invention.

3. Consequently, the two physio-chemical forms of an antigen, as defined in the composition of claim 1, are characterized only by the technical feature that one form is "soluble" while the other form is "insoluble".

The Appellants argue that these terms, in the absence of a definition of the solvent used and the temperature applied, do not allow a skilled person to realize if he/she is working within the scope of protection conferred by the claim. By referring to the case law of

the Boards of Appeal in decisions T 256/87 of 26 July 1988 and T 241/89 of 14 August 1990, they conclude that the invention is not disclosed sufficiently clear and complete for it to be carried out by a skilled person.

4. The Board does not consider these decisions as being applicable in the present case.

Decision T 256/87 deals with claims to a detergent composition comprising a certain amount of enzyme-accessible calcium (EAC). The competent Board decided that the requirements of Article 84 EPC were met as the description provided a clear and consistent definition of what is meant by EAC. Further, the Board decided that, although no direct analytical method for the determination of EAC was disclosed, the skilled person, by applying indirect empirical investigation, was able to know when he was working within the forbidden area of the claims. This was possible because upper and lower limits claimed were correlated with observable phenomena. Accordingly the requirements of Article 83 EPC were met.

The subject-matter underlying decision T 241/89 was also a detergent composition. It contained not more than 3 mg/kg of reactive titanium (IV). The Board, finding that the disclosure of the patent was insufficient insofar as the method for determining the amount of reactive titanium (IV) was concerned, particularly since this parameter was the only one to distinguish the claimed composition from prior art ones, decided that the requirements of Article 83 EPC were not met.

Thus, in both cases the competent Boards had to decide whether or not the patent contained sufficient disclosure, allowing a skilled person to quantitatively determine the amount of a compound being a technical feature of the claimed composition. This requirement had to be fulfilled in order to put the skilled person in a position where he knows when he is working in the forbidden area of the claims, in accordance with the requirements of Article 83 EPC.

5. The situation underlying the present case is different. Solubility is a characteristic of a substance which depends of the conditions under which it is determined. As for instance mentioned in document (13), the particular solvent used and the temperature applied play an important role.

The patent in suit does not disclose the conditions under which the solubility/insolubility of the two forms of an antigen contained in the claimed composition is determined. Thus, no clear definition of the terms "soluble" and "insoluble" is given, which terms therefore are vague and open to interpretation.

Contrary to the situation as described in the case law of the Boards of Appeal discussed in point (4) above, the skilled person is not in a situation where he is unable to determine the parameter in question, because he is not aware of a single method for doing so. In the present case the Board is convinced that the skilled person, on the basis of his general knowledge, is able to determine if an antigen exists in soluble or in insoluble form under specific conditions given. However, in the absence of a clear definition of the

conditions under which the determination is carried out (solvent, temperature) the skilled person is free to choose from a large number of possible conditions when determining solubility/insolubility of the two antigen forms.

6. This may lead to the situation that claim 1 has a very broad scope, but it does not result in lack of sufficiency of disclosure contrary to the requirements of Article 83 EPC, in the sense as established in decision T 241/89 (supra)

7. The absence of a clear definition of the terms "soluble" and "insoluble" used in claim 1, respectively of the conditions under which these characteristics are determined, is considered by the Board to result in a lack of clarity of claim 1.

This cannot be challenged in opposition/appeal proceedings as the requirement that the claims of a European patent shall be clear is laid down in Article 84 EPC, which is not itself a ground for opposition under Article 100(a) EPC. However, questions of clarity or support may affect the decision on issues under Article 100 EPC such as e.g. novelty (Article 54 EPC). If the wording of a claim does not allow a clear distinction of its subject-matter vis-à-vis known subject-matter, Patentee has to be prepared that the claim is interpreted in the broadest possible way.

Novelty (Article 54 EPC)

8. Document (12) discloses a composition for enhancing the immunogenicity of an envelope glycoprotein of a virus, comprising the envelope glycoprotein or a fragment thereof of at least 50 amino acids, and a peptide derived from the envelope glycoprotein which comprises at least one neutralisation epitope (page 2, second paragraph). The word "composition" is intended to comprise a preparation allowing the simultaneous application of the two components (page 2, third paragraph).

The glycoproteins are preferably whole molecules as obtained before possible cleavage (page 12, second full paragraph). The peptides, also designated "amplifiers" can be free or bound to a carrier (page 12, third full paragraph).

9. The Opposition Division stated in the decision under appeal, that document (12) does not contain specific examples showing co-administration of two different forms of an antigen. In view of the fact that document (12) contemplates a number of antigens and combinations of antigens which do not contain a soluble and an insoluble antigen form, they concluded that the general disclosure on page 2 of the less preferred possibility, administering antigens simultaneously or in a mixture, does not anticipate a claim to a composition in accordance with claim 1.

Moreover, they found that in document (12) the term "gp160" is used to designate a glycoprotein obtained from a vaccinia virus VV-1163, coding for the gp160env mutant, which was considered soluble in aqueous solutions as it lacks the transmembrane hydrophobic zone. Consequently, document (12) at the best disclosed compositions comprising two soluble forms of an antigen.

10. The fact that the majority of embodiments disclosed by a prior art document, including the preferred embodiments given in the examples, lie outside the scope of protection of a patent claim under consideration, does not effect that a general disclosure, referring to a less preferred embodiment, which lies within the scope of said claim can be disregarded when examining novelty.

Document (12) explicitly discloses that the preferably used glycoproteins are whole molecules as obtained before possible cleavage (cf page 12). On page 9, first full paragraph it is said that besides gp160env derived from VV-1163, also a version of gp160 containing the hydrophobic transmembrane domain and derived from VV-1139 is used. It is evident for a skilled person that the presence of a hydrophobic domain prevents the solubility of a protein in aqueous media. Thus, document (12) not exclusively refers to envelope glycoproteins soluble in aqueous solutions.

11. The short amplifier peptides according to document (12) are considered to be soluble in aqueous solutions. This is not disputed by the Respondents.

The Board, considering that no clear definition of the terms "soluble" and "insoluble" is given in claim 1 (see points (3) to (7) above), decides that the disclosure of a composition of an envelope glycoprotein and a peptide derived from its amino acid sequence as disclosed in document (12) anticipates the subject-matter of claim 1 of the main request, which accordingly does not meet the requirement of Article 54 EPC.

Auxiliary Request

Allowability of amendments (Articles 123(2) and 123(3) EPC)

12. Claim 1 corresponds to claim 3 as originally filed and thus meets the requirements of Article 123(2) EPC.

By introducing an additional feature into claim 1 as granted, the protection conferred has been restricted with regard to the claims as granted (Article 123(3) EPC).

Clarity (Article 84 EPC)

13. The Appellants objected that claim 1 lacks clarity as it comprises an embodiment wherein the composition contains a soluble, lipidated form and an insoluble, not lipidated form of an antigen.

14. When considering a claim, one should rule out interpretations which are illogical or which do not make technical sense. One should try to arrive at an interpretation of the claim which is technically sensible and takes into account the whole disclosure of

the patent (Article 69 EPC). The claim must be construed by a mind willing to understand not a mind desirous of misunderstanding (cf decision T 396/99, ultimate paragraph of section 3.5).

15. The patent refers to a composition for eliciting an immune response to an antigen in an animal. Lipidated substances are soluble preferably in organic solvents. In the light of the disclosure of the patent as a whole an interpretation of claim 1 as considered possible by the Appellants (cf point (13) above) is technically not sensible.

Sufficiency of disclosure (Article 83 EPC)

16. Compared to claim 1 of the main request, the two forms of an antigen, have been further defined by the technical feature that one form is lipidated and the other form is not lipidated. The patent contains the following examples of such pairs of antigen forms:

- whole inactivated influenza virus and HA(p)
- split HA and HA(p)
- OspA-NL and OspA-L.

The Board is thus convinced that the patent specification puts the skilled person in possession of putting the claimed invention into practice.

Moreover, the Board has no reason to doubt that a skilled person can put the invention into practice over the whole scope of the claim by finding other antigens existing in the two physio-chemical forms required by claim 1. Therefore, the requirements of Article 83 EPC are met.

17. With regard to the use of the terms "soluble" and "insoluble" in claim 1, which are considered to be vague and open to interpretation, the Board refers to points (5) to (7) above.

Novelty (Article 54 EPC)

18. Document (12) discloses compositions comprising an "insoluble" viral envelope glycoprotein and a "soluble" (amplifier-) peptide derived from the amino acid sequence of the envelope glycoprotein (cf points (8) to (11) above).

On page 12, third full paragraph, it is said that the peptides can be associated with other peptides corresponding to T-epitopes, or even to peptides, **lipopeptides**, or others, capable of stimulating the immune system and/or specifically targeting the "amplifier" peptides to antigen-presenting cells.

The mentioning of lipopeptides in this passage of document (12) refers to subject-matter different from the matter of the claims under consideration. A composition comprising an envelope glycoprotein and an amplifier-peptide associated with a lipopeptide, as defined on page 12 of document (12), does not

anticipate the novelty of claim 1 of the auxiliary request.

19. Document (20) discloses the potentiation of poorly immunogenic subunit influenza virus vaccines by a small dose of whole virus vaccine. Hemagglutinin (HA) and neuraminidase (NA) subunit vaccine is prepared from virus particles by disruption with ammonium deoxycholate and administered to unprimed animals and humans together with varying amounts of heterologous and homologous whole virus particles.

It was shown in tables II, III and V that the antibody response to the subunit vaccine could be potentiated by a small dose of whole virus, both in hamsters and seronegative young adults.

Document (21), from the same authors, contains essentially the same teaching.

This state of the art does not disclose a composition according to claim 1, containing two physio-chemical forms of an antigen, characterized in that one is lipidated and the other is not lipidated.

20. The Board decides that the subject-matter of claim 1, and of claims 2 to 4 dependent thereon, is novel and meets the requirements of Article 54 EPC.

Inventive step (Article 56 EPC)

21. In accordance with the problem and solution approach, the Boards of Appeal in their case law have developed certain criteria for identifying the closest prior art

providing the best starting point for assessing inventive step. It has been repeatedly pointed out that this should be a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common , i.e. requiring the minimum of structural modifications (cf Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.D.3.1).

22. While the Appellants consider both, documents (12) and (20) as being suitable starting points for the application of the problem and solution approach, the Board is of the opinion that document (20), disclosing a composition comprising whole virus particles and a subunit vaccine as representing the closest prior art, as it has the same aim as the patent in suit, namely to enhance the immune response of weakly immunogenic materials in naive animals (see patent in suit, page 2, column 1, lines 10 to 12 and lines 44 to 48 and document (20), abstract).
23. In the light of the disclosure in document (20) the technical problem to be solved by the patent in suit is seen as the provision of an alternative vaccine composition.
24. This problem is solved by the composition according to claim 1, comprising two physio-chemical forms of an antigen, wherein the first form is a soluble form and the second form is an insoluble form, and wherein one form is lipidated and the other form is not lipidated.

The remarkably improved effect obtained by co-administration of HA(p) and whole inactivated virus can be seen in Figure 1 of the patent in suit (cf groups 7 and 8).

25. Documents (20) and (21), as well the other prior art documents on file, do neither disclose nor hint at the provision of an antigen in a lipidated and a not lipidated form. Thus, the skilled person does not get any information that would encourage him to further develop the disclosure in the closest prior art and to arrive at the subject-matter of claim 1 in an obvious way.

Claims 1 to 4 of the auxiliary request are based on an inventive step and meet the requirements of Article 56 EPC.

Order

For these reasons it is decided:

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to maintain the patent on the basis of the following documents:

claims: 1 to 4 filed during oral proceedings on
14 September 2004 as auxiliary request

description: pages 2 and 3 filed during the oral
proceedings, pages 4 and 5 as granted

Figures: 1 to 9 as granted

The Registrar:

The Chairwoman:

P. Cremona

U. Kinkeldey