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Datasheet for the decision of 17 February 2022

Case Number: T 1835/19 - 3.3.04

Application Number: 11768133.8

Publication Number: 2613806

IPC: A61K39/095, C07K14/22

Language of the proceedings: EN

Title of invention:
Non-lipidated variants of Neisseria meningitidis ORF2086 antigens

Patent Proprietor:
Wyeth LLC

Opponent:
Mathys & Squire LLP

Headword:
N. meningitidis antigens/WYETH

Relevant legal provisions:
EPC Art. 54(2), 84

Keyword:
Novelty - main request (no) - auxiliary requests 1 to 7 (no)
Claims - clarity - auxiliary request 8 (no)

Decisions cited:
G 0001/04

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 1835/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 17 February 2022

Appellant: (Patent Proprietor)	Wyeth LLC 235 East 42nd Street New York, NY 10017-5755 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Respondent: (Opponent)	Mathys & Squire LLP The Shard 32 London Bridge Street London SE1 9SG (GB)
Representative:	Wilding, James Roger Mathys & Squire The Shard 32 London Bridge Street London SE1 9SG (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 23 April 2019 concerning maintenance of the European Patent No. 2613806 in amended form.**

Composition of the Board:

Chair	A. Chakravarty
Members:	B. Rutz
	L. Bühler

Summary of Facts and Submissions

I. The appeal by the patent proprietor (appellant) lies from the opposition division's interlocutory decision to maintain European patent No. 2 613 806 in amended form based on auxiliary request 8 filed during oral proceedings. The patent is entitled "*Non-lipidated variants of Neisseria meningitidis ORF2086 antigens*". The opponent is respondent to the appeal.

II. The patent was opposed on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and of Article 100(b) EPC and Article 100(c) EPC.

III. In the decision under appeal, the opposition division decided that the main request (claims as granted) complied with the requirements of Article 123(2) EPC, but that the subject-matter of claims 1, 3 and 10 was not novel over the disclosure in document D1 (Article 54 EPC). The subject-matter of auxiliary requests 1 to 4 lacked novelty for the same reasons as that of the main request.

Claim 1 of auxiliary request 6, was held not to be clear (Article 84 EPC). The claims of auxiliary request 7, were held not to be concise (Article 84 EPC).

Finally, auxiliary request 8 was held to comply with the requirements of the EPC.

IV. With the statement of grounds of appeal, the appellant maintained the claims as granted as the main request and re-filed sets of claims of auxiliary requests 1 to

6, 8 and 9 and filed a new set of claims of auxiliary request 7.

V. Auxiliary request 1 is identical to auxiliary request 1 dealt with in the decision under appeal. Auxiliary requests 2 and 3 are identical to auxiliary requests 1a and 1b, respectively, filed with letter of 7 September 2018, but not dealt with in the decision under appeal. Auxiliary requests 4 to 6 are identical to auxiliary requests 2 to 4, respectively, dealt with in the decision under appeal. Auxiliary request 7 is identical to auxiliary request 4, dealt with in the decision under appeal, except that granted claims 3 and 10 have been cancelled. Auxiliary requests 8 and 9 are identical to auxiliary requests 6 and 8, respectively, dealt with in the decision under appeal.

VI. Claim 1 of the patent as granted reads:

"1. A composition comprising an isolated non-pyruvylated non-lipidated ORF2086 polypeptide, wherein the polypeptide comprises the amino acid sequence selected from the group consisting of SEQ ID NO:13, SEQ ID NO:18 and SEQ ID NO: 21, wherein the cysteine at position 1 is deleted."

Claim 1 of auxiliary requests 1, 4, 5 and 7 differs from claim 1 of the main request in that the composition is defined as "immunogenic".

Claim 1 of auxiliary request 2 differs from claim 1 of auxiliary request 1 in that it has the additional feature "and wherein said polypeptide is isolated from a bacterial cell".

Claim 1 of auxiliary request 3 differs from claim 1 of auxiliary request 1 in that it has the additional feature "and wherein said polypeptide is isolated from an *E. coli* cell".

Claim 1 of auxiliary request 8 reads:

"An immunogenic composition comprising an isolated non-pyruvylated non-lipidated subfamily A ORF2086 polypeptide, comprising the amino acid sequence of SEQ ID NO:13, wherein the cysteine at position 1 is deleted and an isolated non-pyruvylated non-lipidated subfamily B ORF2086 polypeptide, wherein the subfamily A protein to subfamily B protein ratio is 1:1."

VII. The board appointed oral proceedings and informed the parties of its preliminary opinion on the appeal case in a communication pursuant to Article 15(1) RPBA.

VIII. In this communication, the board informed the parties that it was of the preliminary view that the subject matter of claim 1 of the main request and of auxiliary requests 1 to 7 was not novel over the disclosure in document D1 (see section X.) and that claim 1 of auxiliary request 8 lacked clarity.

IX. Oral proceedings before the board took place on 16 February 2022 by videoconference as requested by the parties. At the end of the oral proceedings, the Chair announced the board's decision.

X. The following documents are cited in the present decision:

D1 WO03/063766

D7 Jiang et al., Vaccine (2010); 28:6086-6093.

D8 Giuliani et al., PNAS (2006); 103(29): 10834-10839.

XI. The appellant's arguments are summarised as follows:

Main request and auxiliary requests 1 and 4 to 7
Novelty (Article 54 EPC) - claim 1

Document Dl was not relevant to the novelty of the subject-matter of claim 1 because it did not make the subject-matter of the invention available to the skilled person in the form of a technical teaching. Specifically, it did not disclose an example of the production of a non-pyruvylated non-lipidated polypeptide as claimed.

As it was not known at the relevant date that pyruvylation occurred at the N-terminal cysteine, which was also the site of lipidation, no link between lipidation status and pyruvylation status could have been made by the skilled person reading document D1 alone or together with common general knowledge.

Pyruvylation was also not an inherent feature of the sequences of document D1, because the respective polypeptides had not been expressed in any host.

Pyruvylation only occurred upon extrinsic interaction of the primary translation product in the host cell

expressing the protein (i.e. post-translational modification). Such post-translational modification could only be ascertained upon expression and examination of the successfully expressed protein and thus should not be considered as inherently disclosed with the sequence information as provided in document D1. Document D1 disclosed many different processes and it was not inevitable that all of these lead to the expression of "non-pyruvylated" polypeptides.

Moreover, even in the absence of an N-terminal cysteine, pyruvylation might occur at other sites in the polypeptide.

Thus, in the absence of a direct and unambiguous disclosure in document D1 of the process by which the sequences of SEQ ID NOs: 60 and 228 were expressed, there was no disclosure of the non-lipidated, non-pyruvylated versions of these polypeptides.

Auxiliary requests 2 and 3
Novelty (Article 54 EPC) - claim 1

Pyruvylation only occurred upon extrinsic interaction of the translation product in the host cell expressing the protein and thus was not inherently disclosed with the sequence information provided in document D1.

Auxiliary request 8
Clarity (Article 84 EPC) - claim 1

In the decision under appeal, the opposition division held that the lack of definition of the weight or molar values to calculate the ratio in claim 1 rendered the scope of the claim unclear. The patent, however, made it clear that only a weight ratio could be meant. All

doses of antigens in the patent were expressed in terms of weight (i.e. in µg); in particular: page 20, paragraph [0126]; example 11,page 31, line 53, Table 9 (left column), page 32, line 12, Table 10 (left column); example 12, page 32, line 40, Table 12 (page 33, fifth column) and Table 14 (page 33-34 third column).

In contrast, the patent never mentioned a molar dose or a molar ratio in relation to the dose of antigens. In view of this, the skilled person would have understood the ratio of antigens referred to in paragraph [0103] to be a weight ratio.

This view was supported by documents D7 and D8, which showed that in the field of biopharmaceuticals (e.g. proteins), a weight to weight ratio was standard (see document D7, page 6087, right-hand column, first paragraph and document D8, page 10838, paragraph bridging columns).

XII. The respondent's arguments are summarised as follows:

Main request and auxiliary requests 1 and 4 to 7
Novelty (Article 54 EPC) - claim 1

The claimed subject-matter lacked novelty in the light of the disclosure in document D1 of the expression of the amino acid sequences of SEQ ID NO: 60 and 228. The ORF2086 polypeptides produced were inevitably both non-pyruvylated and non-lipidated, because they had no cysteine residues (N-terminal or otherwise).

There was no need for further evidence on the pyruvylation state of the ORF2086 polypeptide sequences of SEQ ID NOs: 60 or 228 of document D1, as the patent

itself explained (see paragraph [0064] and Example 10) that these polypeptides had to be non-pyruvylated due to their lack of any cysteine residues. In this respect, the leader sequence was irrelevant as it was cleaved from the mature protein. That the composition and internal structure of a marketed product forms part of the state of the art where the skilled person can discover its composition or internal structure and therefore reproduce the product without undue burden was settled by the Enlarged Board of Appeal in decision G 1/92. In the present case, the skilled person did not even have to investigate the internal structure of the the polypeptides disclosed in document D1 because all the necessary information, i.e. the sequences of SEQ ID NO: 60 and 228, was available in document D1 itself. This view was supported by paragraph [0195] of the patent which reported that the A05 polypeptide (identical to SEQ ID NO: 60 of document D1) contained no detectable pyruvylation.

Auxiliary requests 2 and 3
Novelty (Article 54 EPC) - claim 1

Document D1 generally disclosed isolation of the ORF2086 polypeptides from bacterial cells, including *E. coli*. (see page 1 at lines 2 to 6; page 47 at line 1; page 49 at lines 1 to 3 and 11 to 13; page 69 at lines 5 and 19 to 25; and Example 3 at page 86, line 19). The claimed subject-matter therefore lacked novelty.

Auxiliary request 8
Clarity (Article 84 EPC) - claim 1

It was unclear how the 1:1 ratio specified in claims 1 and 2 was to be calculated. It might be common practice to express doses administered to patients in weight

amounts, but the feature at issue was a ratio, not a dose. It was equally common practice to express ratios as molar ratios. The expression "1:1 ratio" therefore rendered the claim unclear.

XIII. The appellant (patent proprietor) requested that the decision under appeal be set aside and the opposition be rejected (main request) or alternatively, that the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 1 to 9 filed with their statement of grounds of appeal.

The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is admissible.

Main request and auxiliary requests 1 and 4 to 7
Novelty (Article 54 EPC) - claim 1

2. Claim 1 of the patent as granted is for a "composition comprising an isolated non-pyruvylated non-lipidated ORF2086 polypeptide polypeptide, wherein the polypeptide comprises the amino acid sequence selected from the group consisting of SEQ ID NO: 13, SEQ ID NO:18 and SEQ ID NO: 21, wherein the cysteine at position 1 is deleted".

3. Document D1 discloses ORF2086 polypeptides with, *inter alia*, the amino acid sequences SEQ ID NO: 60 and SEQ ID NO: 228. It is undisputed that these peptides correspond to SEQ ID NO: 13 and 18 referred to in the claim, except that they contain a methionine instead of

a cysteine at the N-terminus, i.e. the cysteine is deleted. It is also undisputed that due to the absence of an N-terminal cysteine, the above mentioned peptides are non-lipidated. Document D1 also discloses compositions comprising these peptides (see claims 60(a), 66 and 71).

4. The appellant challenges the opposition division's finding of lack of novelty, arguing that non-pyruvylation was not an inherent feature of the polypeptides with sequences SEQ ID NOs: 60 and 228 in document D1. The appellant reasoned that there was no disclosure in document D1 that the polypeptides had been expressed in a host organism and, since pyruvylation occurred post-translationally, there was no disclosure of non-pyruvylated versions of the polypeptides.

5. The board recognises that document D1 does not mention the pyruvylation status of any of the disclosed polypeptides. However, the relevant polypeptides disclosed in document D1 are non-lipidated and non-pyruvylated due to their lack of a cysteineon which those modifications could occur.

6. Document D1 discloses the non-lipidated form of ORF2086 polypeptides (referred to as "2086 proteins" in document D1) on page 49, lines 11 to 13, which reads "[t]*he non-lipidated form is produced by a protein lacking the original leader sequence or a* [sic] *by a leader sequence which is replaced with a portion of sequence that does not specify a site for fatty acid acylation in a host cell*". Furthermore, the expression of the non-lipidated form of a 2086 protein is disclosed in Example 3 which reads: "*to further evaluate the immunogenicity of the 2086 protein,*

cloning and expression of the non-lipidated form of P2086 were performed" (see page 85, lines 20 to 21), "*amplify the 2086 gene with an ATG (Met) fused to the second amino terminal codon (ACG) representing a single amino acid substitution (replaces TGC Cys) of the mature 2086 polypeptide*" (see page 86, lines 8 to 11), "*plasmid DNA was used to transform the expression strain BLR(DE3)pLysS*" (see page 88, line 2), "*rP2086T7 gene fusions were transformed into BLR(DE3)pLysS, selected on Terrific Broth/Kan plates, grown in Terrific Broth and induced to express the rP2086T7 fusion protein*" (see page 87, lines 15 to 17) and "[t]*his purified fusion protein was used to immunize mice and generated significant levels of bactericidal antibodies against a heterologous meningococcal strain. (See Table V)*" (see page 88, lines 7 to 9).

7. Taken as a whole, document D1 discloses the production of non-lipidated 2086 proteins, including SEQ ID NO: 60 and 228, by transforming *E. coli* with a plasmid carrying a coding sequence lacking the codon for an N-terminal cysteine. The resulting proteins are devoid of cysteine residues, including an N-terminal cysteine and are non-pyruvylated, as confirmed by the disclosure in the patent, as explained below.

8. The patent states that "*deletion of the N-terminal Cys from the non-lipidated P2086 variant sequences avoided pyruvylation of non-lipidated P2086 variants*" (see paragraph [0064]) and "[w]*hen A05 (SEQ ID NO: 13 wherein the N-terminal Cys at position 1 is deleted or SEQ ID NO: 55) and B44 variants (SEQ ID NO: 21 wherein the N-terminal Cys at position 1 is deleted or SEQ ID NO: 44), which do not contain an amino-terminal cysteine, were purified, there was no detectable pyruvylation (+70 Da)*" (see paragraph 0195]). The

patent itself thus confirms that expression of the polypeptide of SEQ ID NO: 13 wherein the N-terminal cysteine at position 1 is deleted (identical to SEQ ID NO: 60 as disclosed in document D1), inevitably leads to a non-pyruvylated polypeptide.

9. The appellant also did not identify any specific process disclosed in document D1 which would lead to pyruvylation of SEQ ID NO: 60 or 228 upon expression.

10. In conclusion, document D1 discloses expression of the ORF2086 polypeptides with the amino acid sequence of SEQ ID NO: 60 and 228 in *E. coli* and their isolation. The mature polypeptide contains no N-terminal cysteine (or any other cysteine) and is thus neither lipidated nor pyruvylated.

11. Thus the board agrees with the opposition division that "*non-pyruvylation is an inherent feature to the non-lipidated polypeptides of SEQ ID NOs:60 and 228 which also lack a Cys residue*".

12. The subject-matter of claim 1 lacks novelty over the disclosure of document D1 (Article 54 EPC).

Auxiliary requests 2 and 3
Novelty (Article 54 EPC) - claim 1

13. The subject-matter of claim 1 of these requests, which were not considered in the decision under appeal, also lacks novelty over the disclosure in document D1 of ORF2086 polypeptides (SEQ ID NO: 60 and 228) and their expression in bacterial cells, including *E. coli*, for the same reasons as outlined for the main request above. The appellant has not argued that the host system "bacterial" or "*E. coli*" was relevant for the

non-pyruvylation or conferred additional properties to the polypeptide. In view of the disclosure in the patent, the absence of pyruvylation depends on the missing N-terminal cysteine residue alone and additional technical features are neither disclosed nor required. Furthermore, expression of ORF2086 polypeptides in *E. coli* is disclosed in document D1 (see page 1 at lines 2 to6; page 47 at line 1; page 49 at lines 1 to 3 and 11 to 13; page 69 at lines 5 and 19 to 25; and Example 3 at page 86, line 19).

Auxiliary request 8
Clarity (Article 84 EPC) - claim 1

14. The feature "the subfamily A protein to subfamily B protein ratio is 1:1" in claim 1 is not clear because the property from which to calculate the ratio is not defined (see decision under appeal, sheet 11, points 1 to 4). The argument of the appellant that "*the skilled person would understand in view of the ample and consistent use of a weight unit in the Patent and the absence of the use of a molar unit that the ratio of antigens referred to in paragraph [0103] clearly implies a weight ratio*" is not convincing because the use of weight units in the patent does not imply that the skilled person would have considered that a 1:1 ratio could only be a weight/weight ratio and not, for example, a molar ratio, since both fall within the ordinary meaning of the term.

15. Moreover, the board has not seen any convincing reason why a molar ratio would be ruled out by the skilled person. Indeed a 1:1 molar ratio makes technical sense since the claim defines the subfamily A protein as "comprising the amino acid sequence of SEQ ID NO:13". The protein can therefore be longer than the amino acid

sequence of SEQ ID NO: 13, including for instance, fusion proteins (see patent paragraph [0130]), dimers, multimers, additions (see patent paragraph [0057]) and Gly/Ser stalks (see patent paragraphs [0019] and [0065]), while the subfamily B protein (which is not defined by a specific sequence in the claim) also includes fragments and deletions (see patent paragraph [0057]). Thus the subfamily A and B proteins in the composition can vary substantially in size. The skilled person would have considered a molar ratio as a technically sensible interpretation, for example when aiming to have an equal number of epitopes for each subfamily. This renders the claim unclear because it leaves the person skilled in the art in doubt which definition to choose.

16. The appellant further argued that it was common general knowledge, supported by the disclosure in the patent, that in the field of pharmaceuticals and in particular proteins (antigens), ratios were expressed as weight/ weight ratios (see section XI. above).

17. These arguments do not convince the board because neither the patent itself nor the cited scientific articles represent an objective and complete summary of the common general knowledge at the relevant date.

18. Moreover, a claim should be clear from its wording alone (G 1/04, OJ EPO 2006, 334, point 6.2 of the Reasons and Case Law of the Boards of Appeal, 9th edition, 2019, II.A.3.1).

Auxiliary request 9

19. The board notes that present auxiliary request 9 corresponds to the appellant's former auxiliary

request 8 on which the interlocutory decision under appeal maintaining the patent as amended was based.

20. As the patent proprietor is the sole appellant, the principle of "prohibition of *reformatio in peius*" applies. The board is therefore not empowered to deal with this request.

Conclusion

21. As neither the main request nor any of auxiliary requests 1 to 8 are allowable, the appeal must be dismissed. The maintenance of the patent as amended in accordance with auxiliary request 9 may not be challenged.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

I. Aperribay A. Chakravarty

Decision electronically authenticated