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Datasheet for the decision of 9 November 2021

Case Number: T 1713/19 - 3.3.04

Application Number: 11769799.5

Publication Number: 2753352

IPC: A61K39/08, C07K14/33

Language of the proceedings: EN

Title of invention:
Isolated polypeptide of the toxin A and toxin B proteins of C. difficile and uses thereof

Patent Proprietors:
Valneva Austria GmbH
Valneva USA, Inc.

Opponent:
GlaxoSmithKline Biologicals SA

Headword:
Toxin A-Toxin B fusion/VALNEVA

Relevant legal provisions:
EPC Art. 54(2), 54(3), 56, 83, 123(2), 123(3)
EPC R. 103(4)(a)

Keyword:
Amendments - added subject-matter (no) - broadening of claim (no)
Novelty - (yes)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

Decisions cited:
G 0001/03, T 0725/08, T 0759/10, T 2134/10, T 0107/14

Catchword:
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Case Number: T 1713/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 9 November 2021

Respondent: (Patent Proprietor 1)	Valneva Austria GmbH Campus Vienna Biocenter 3 1030 Vienna (AT)
Respondent: (Patent Proprietor 2)	Valneva USA, Inc. 910 Clopper Road, Suite 160S Gaithersburg, MD 20878 (US)
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Representative:	Johnston, Caroline Louise GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 9 April 2019 concerning maintenance of the European Patent No. 2753352 in amended form.**

Composition of the Board:

Chair	B. Claes
Members:	B. Rutz
	R. Romandini

Summary of Facts and Submissions

I. Appeals were lodged by the patent proprietors (appellants I) and the opponent (appellant II) against the interlocutory decision of the opposition division finding that European patent No. 2 753 352 ("the patent") as amended in accordance with auxiliary request 1 complied with the EPC. The patent is entitled "*Isolated polypeptide of the toxin A and toxin B proteins of C. difficile and uses thereof*". The patent was granted for a European patent application which had been filed as an international application published as WO 2012/028741 ("the application").

II. Claims 1, 2 and 9 of auxiliary request 1 read:

"1. An immunogenic or vaccine composition comprising an isolated polypeptide having at least 86% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 4 and a pharmaceutically acceptable carrier or excipient.

2. The composition of claim 1, wherein said polypeptide provides 100% survival of hamsters vaccinated with said polypeptide after intragastric administration of a dose of 10^2, 10^3 and 10^4 *Clostridium difficile* spores.

9. An isolated polypeptide having at least 86% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 4, or the composition of any one of claims 1 to 8, for use in the prevention or treatment of a *C. difficile* associated disease (CDAD)."

III. The opposition proceedings were based on the grounds in Article 100(a) EPC, in relation to novelty

(Article 54 EPC) and inventive step (Article 56 EPC), and in Article 100(b) and (c) EPC.

IV. The opposition division decided that the claims of auxiliary request 1 complied with the requirements of Article 123(2) and (3) EPC, the claimed subject-matter was novel and involved an inventive step, and the claimed invention was sufficiently disclosed in the patent.

V. With their statement of grounds of appeal, appellants I maintained the main claim request of the opposition proceedings (patent as granted) and submitted three auxiliary requests.

VI. Appellant II filed its statement of grounds of appeal.

VII. In reply to the appeal of appellant II, appellants I submitted 13 further auxiliary requests; auxiliary request 4 being identical to auxiliary request 1 held allowable by the opposition decision.

VIII. Appellant II replied to the appeal of appellants I.

IX. The board summoned the parties to oral proceedings as requested and informed them of its preliminary opinion in a communication pursuant to Article 15(1) RPBA.

X. In reply to the board's communication, appellants I made auxiliary request 4 their main request.

XI. During the oral proceedings, the patent proprietors (former appellants I, in the following, "respondents") withdrew their appeal. At the end of the oral proceedings, the Chair announced the board's decision.

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

D1 WO 2010/017383

D3 I. F. Belyi and N. A. Varfolomeeva, "*Construction of a fusion protein carrying antigenic determinants of enteric clostridial toxins*", FEMS MICROBIOLOGY LETTERS 225(2), 2003, 325-329.

D4 WO 2012/163817

D6 WO 2011/60431

D9 G. S. Tillotson and J. Tillotson, "*Clostridium difficile - a moving target*", F1000 Medicine Reports 3:6, 2011.

D12 BLASTP Alignment between SEQ ID NO: 4 and SEQ ID NO: 21 of document D1

D18 BLASTP Alignment between SEQ ID NO: 4 and SEQ ID NO: 6 of document D4

XIII. The appellant's (opponent's) arguments are summarised as follows.

Main request
Claim construction - claims 1 and 9

In the expression "an isolated polypeptide having at least 86% sequence identity to the amino acid sequence

as set forth in SEQ ID NO: 4", "having" had to be interpreted, according to common language use, as "comprising". This meant that the isolated polypeptide could *comprise* a sequence with 86% sequence identity. This was also evident from claim 5 of the application which was dependent on claim 1 and referred to, *inter alia,* SEQ ID NO: 18 and 20, which were longer sequences than SEQ ID NO: 4 ("*wherein the polypeptide is selected from the group consisting of SEQ ID: 2, SEQ ID NO: 4, SEQ ID NO. 18, SEQ ID NO: 20*").

Furthermore, according to the claims' wording, SEQ ID NO: 4 was the sequence to be compared to sequences in the art. It was therefore the length of this sequence (SEQ ID NO: 4 of the patent) which had to be used as the denominator to calculate the percent identity of the claimed polypeptide.

Amendments (Article 123(2) EPC) - claims 1 and 9

The subject-matter of claim 1 could not be derived directly and unambiguously from the application.

Paragraph [0187] disclosed "*isolated polypeptides of the present invention may have at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity or sequence similarity with SEQ ID NO: 2 or SEQ ID NO: 4*". This, however, represented a large number of possible combinations from three different lists (i.e. 15 different percentage values, sequence identity or similarity and SEQ ID NO: 2 or SEQ ID NO: 4). The selection of one combination from these resulted in added subject-matter. The paragraph, furthermore, did not disclose other features such as "immunogenic or vaccine

composition" and "pharmaceutically acceptable carrier or an excipient".

Also, the remaining parts of the application did not disclose an isolated polypeptide comprised in an "immunogenic or vaccine composition" in combination with a "pharmaceutically acceptable carrier or an excipient".

The application did not, in fact, disclose a "vaccine composition".

Should the wording in claim 1, i.e. "an isolated polypeptide having at least 86% sequence identity ...", be interpreted as a polypeptide which consists of a sequence having at least 86% sequence identity (see discussion of "*Claim construction*" above), a basis for this new meaning was equally lacking in the application as filed. Paragraph [0117], for example, described an isolated polypeptide comprising SEQ ID NO: 4.

The application did not disclose the following features of claim 9:
(1) the polypeptide for prevention or treatment of a CDAD being isolated
(2) the use being for the prevention or treatment of a CDAD
(3) an immunogenic or vaccine composition being used in the prevention or treatment of a CDAD.

Paragraph [0119] did not disclose the isolated polypeptide being used in the prevention or treatment of a CDAD but related to "*one or more symptoms of CDAD*". Furthermore, the method disclosed in that passage was limited to administration of the polypeptide "*to a subject in need thereof*".

Extension of scope of protection (Article 123(3) EPC) - claim 2

Claim 2 as granted provided for a 100% survival rate after challenge with only one of the three doses (the "or" meant three alternatives), whereas the claim now provided for a 100% survival rate after challenge with all three doses. The amendment thus amounted to an extension of the scope of protection of the patent.

Novelty (Article 54 EPC) - claim 1

The alignment in document D12 showed that SEQ ID NO: 4 of the patent and SEQ ID NO: 21 of document Dl shared 99.27% identity across the length of SEQ ID NO: 4 and the alignment in document D18 showed that SEQ ID NO: 4 of the patent and SEQ ID NO: 6 of document D4 shared 94.15% identity across the length of SEQ ID NO: 4.

The subject-matter of claim 1 thus lacked novelty in view of the disclosure of documents D1 and D4.

Sufficiency of disclosure (Article 83 EPC)

The patent disclosed only one way to connect toxins A and B, namely a four amino acid linker (RSMH) between toxins A and B.

There was no teaching in the patent on alternative variants as toxin B was always kept identical, while toxin A was only changed in two amino acids. Variants from other *C. difficile* strains provided only very limited variability as they differed only in few amino acids.

Document D3, which disclosed a fusion protein containing 10 repeats of toxin A linked to about 15 repeats of toxin B as well as *C. perfringens* enterotoxin, demonstrated the difficulty of making a fusion protein which could be stably expressed, as required for a vaccine (see Figure 1). There was no teaching in the patent where the 134 amino acid substitutions allowed by 86% identity could occur in the fusion protein. In view of the deleterious effect of such substitutions on the folding of the protein and the exposure of epitopes, it constituted an undue burden to the skilled person to identify such positions.

Because of the known problems concerning the stability and immunogenicity of *C. difficile* toxin A/toxin B fusion proteins and the lack of teaching in the patent of more than one way to join the toxins to form a fusion protein, the skilled person was unable to work the claimed invention without undertaking a research programme.

The patent did not disclose the medical use of fusion proteins containing up to 134 amino acid differences compared to SEQ ID NO: 4 in claim 9 in a manner sufficiently clear and complete for it to be carried out by the skilled person.

Inventive step (Article 56 EPC)

The disclosure in document D1 represented the closest prior art for the subject-matter of claim 1. The difference between the proteins of SEQ ID NO: 21 of document Dl and of SEQ ID NO: 4 was the presence of a ClyA signal and a longer section of toxin A repeats (39 instead of 19) in the former. The technical problem

identified by the opposition division as "*the provision of a C. difficile immunogenic composition that has neutralising properties against the toxins*" was not solved across the whole breadth of the claim. Therefore, a less ambitious technical problem had to be formulated, i.e. "*the provision of an alternative C. difficile fusion protein*".

Document D1 suggested using shorter fragments (see e.g. paragraph [0041]) and isolated or purified recombinant proteins which would not require the ClyA signal (see e.g. paragraph [0012]). The skilled person knew that the ClyA sequence could be omitted as it was only required for proteins secreted from *Salmonella* but not for isolated proteins. Recombinant fusion proteins of *C. difficile* toxin A and toxin B were known from, for example, documents D2, D3 and D5. The omission of the ClyA sequence thus only replicated known toxin A/ toxin B fusion proteins. The claimed composition was thus obvious in view of the disclosure of document Dl.

Document D6 disclosed a vaccine against *C. difficile* using the repeat domains of either toxin A or toxin B fragments (see title and summary of invention on page 7) which were very similar to the fragments present in the claimed fusion polypeptides. Document D6 described a fragment of toxin A which contained amino acids 2389 to 2710 (see Figure 1 and page 12, lines 20 to 28), i.e. only slightly shorter than the toxin A fragment of SEQ ID NO: 4. The fragment was considered as "*eliciting a balanced and robust mucosa as well as serum neutralizing antibody response*" (see bottom of page 11). The skilled person would therefore have substituted the fragment of toxin A of the fusion protein of document Dl with the fragment of toxin A disclosed in document D6 and thus achieved a

polypeptide having at least 86% identity to SEQ ID NO: 4.

The subject-matter of claim 1 thus lacked an inventive step in view of a combination of the disclosures in documents D1 and D6.

XIV. The respondents' (patent proprietors') arguments are summarised as follows.

Main request
Claim construction - claims 1 and 9

The expression "isolated polypeptide having at least 86% sequence identity" required the claimed polypeptide as a whole (and not merely a subsequence of it) to have at least 86% sequence identity to SEQ ID NO: 4.

The correct way of calculating the percentage of identity thus involved the longer of the two sequences as the reference, i.e. as the denominator.

Amendments (Article 123(2) EPC) - claims 1 and 9

Basis for claim 1 was disclosed, *inter alia,* on page 89, item 2 in combination with page 92, item 1c of the application. From paragraph [0100] onwards, the disclosure was directed to immunogenic or vaccine compositions comprising the isolated polypeptides. Therefore, the combination of the feature "immunogenic or vaccine composition" with the isolated polypeptides did not extend beyond the content of the application.

A specific degree of sequence identity (here 86%) was not a property that, in combination with a specific amino acid sequence, could single out a particular

molecule or confer properties to the claimed subject-matter not derivable from the application (see e.g. decision T 2134/10).

The word "comprising" encompassed the meaning "consisting of", and thus item 2 on page 89 of the application disclosed a polypeptide "having" a certain sequence identity. Alternative basis for a "polypeptide having at least 86% sequence identity to SEQ ID NO: 4" was disclosed in paragraphs [131] and [0187].

Claim 9 combined the subject-matter of claim 1 with the "use in the prevention or treatment of a *C. difficile* associated disease (CDAD)". Paragraph [0128] explicitly referred to the use of immunogenic compositions to prevent or treat CDAD.

Extension of scope of protection (Article 123(3) EPC)

No arguments were submitted in this regard.

Novelty (Article 54 EPC) - claim 1

When the sequence identity between the sequence of SEQ ID NO: 4 of the patent and the sequences of SEQ ID NO: 21 disclosed in D4 or SEQ ID NO: 6 disclosed in D1 was calculated by using the length of the longer sequence as the denominator, these sequences had less than 86% sequence identity. The subject-matter of claim 1 was thus novel.

Sufficiency of disclosure (Article 83 EPC)

No evidence had been provided that the claimed invention could not be performed.

The patent taught, *inter alia*, in paragraphs [0040] and [0060] to [0065], how to produce variants of SEQ ID NO: 4 having at least 86% sequence identity with it. The patent explained how to make variants having a limited number of changes in the amino acid sequence without affecting the activity, function or shape of the isolated polypeptide (see especially paragraph [0069]).

Even if a skilled person were to solely rely on mutations derived from other strains, variants having more divergence in sequence identity from SEQ ID NO: 4 could be generated by combining individual mutations from different strains.

Paragraph [0066] of the patent explained that the toxin A and toxin B regions might be fused directly together without a linker or may be spaced apart by a linker of e.g. 1, 2, 3 ... or 50 amino acids (see paragraph [0080]). Thus, a skilled person could provide such alternative linker sequences (or no linker) to join the two fragments.

Compared to the fusion protein defined in claim 1, document D3 related to a different structure which comprised about 10 toxin A repeats, about 15 toxin B repeats and the *C. perfringens* enterotoxin. The document was thus not suitable to substantiate doubts about the stability of the claimed fusion proteins.

Inventive step (Article 56 EPC)

When starting from the disclosure in document D1, which represented the closest prior art, the objective technical problem was to provide a polypeptide and vaccine composition which could be easily produced and

was highly immunogenic and safe and protective against *C. difficile* infection in humans, including in elderly subjects.

None of the cited documents, and in particular not in documents D1, D3 and D6, taught a skilled person that this problem could be solved using an isolated polypeptide based on sequences with a high degree of sequence identity to SEQ ID NO: 4. It was neither known how many toxin A and toxin B repeats were required in the fusion protein for protective efficacy, nor that neutralising antibodies and a protective effect could be achieved if the ClyA tag was removed.

Therefore, the subject-matter of claim 1 involved an inventive step.

XV. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked in entirety.

The patent proprietors (now the respondents) requested that the appeal of the appellant be dismissed.

Reasons for the Decision

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

Main request
Claim construction - claims 1 and 9

2. The parties dispute the interpretation of the expression "an isolated polypeptide having at least 86%

sequence identity to the amino acid sequence as set forth in SEQ ID NO: 4" (see section II).

3. A first aspect of this interpretation is whether "having at least 86% sequence identity" means that the isolated polypeptide can *comprise* a sequence with 86% sequence identity, as argued by the appellant, or in fact *consists of* a sequence with 86% sequence identity, as argued by the respondents. The opposition division found in this respect with regard to the then main request "*that the wording 'polypeptide having at least 85% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 4' is to be construed to concern proteins which in their full length sequence display at least 85% identity to the full length of SEQ ID NO: 4".*

4. The word "having" can have two different meanings depending on the context:

(i) when referring to *components of an object,* it usually means "comprising" (e.g. "a car having an engine" or "a dog having a tail")
(ii) when referring to *a quality of an object,* it usually refers to the object as a whole (e.g. "a car having red colour" or "a dog having long hair")

In the expression under dispute, a quality of the isolated polypeptide is defined ("86% sequence identity") and, hence, this quality, in the context of the invention, is interpreted by the skilled person as applying to the whole of the isolated polypeptide and not only to parts of it.

5. The appellant's argument that since claim 5 of the application was dependent on claim 1 and included longer sequences than SEQ ID NO: 4, "having" should

mean "comprising" is not persuasive. In fact, claim 1 of the application is directed to "*polypeptides comprising an amino acid sequence having at least 85% ... sequence identity to the amino acid sequence as set forth in SEQ ID NO: 4*" (underlining added by the board). In contrast to the "composition comprising an isolated polypeptide having at least 86% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 4" (underlining added by the board) of this claim , claim 1 of the application encompasses polypeptides with longer sequences, including those "comprising" the sequence of SEQ ID NO: 4.

6. A second aspect of the interpretation concerns the calculation of the sequence identity given that the patent provides no instruction in this regard. Here, the appellant considered that the identity had to be calculated "*across the length of SEQ ID NO:4*".

7. The skilled person reading "having at least 86% sequence identity" would, in the absence of further instructions, give this expression its common meaning. The common understanding of two objects having a certain degree of identity is that they have a number of features in common while differing in a number of other features. The difference can be features present or absent in one object compared to the other, i.e. the difference can be the result of missing or added features. An everyday example would be an original text and its amended version. Certain words might be missing after the amendment, and other words might have been added. In common understanding, striking out half of the words of the text would, however, not lead to the conclusion that the shorter amended text is still 100% identical to the original text, but that it is only 50% identical.

8. To calculate the percentage of identity of two sequences, the board considers it therefore necessary to take both missing and added amino acids into account. This can only be achieved when using the longer of the two sequences as the comparator in respect to which the identity is calculated. Otherwise, the result would be that short sequences that are highly similar to only part of the reference sequence defined in the claim would fall under the definition of the claim. Such an interpretation would (in addition to the fact that it goes against common sense - see the text example above) be dismissed by the skilled person for not being technically meaningful.

9. The board notes in addition that both claims require that the isolated polypeptide having a certain sequence identity should also achieve a function, i.e. be suitable as an "immunogenic composition or vaccine" (claim 1) or "for use in the prevention or treatment of a *C. difficile* associated disease (CDAD)" (claim 9). Short sequences (e.g. consisting of only a few amino acids) which are identical to a short subsequence of SEQ ID NO: 4 are highly unlikely to achieve this function.

10. The board thus agrees with the opposition division that the expression "*is to be construed to concern proteins which in their full length sequence display at least* [X] *% identity to the full length of SEQ ID NO 4*". In practice, this means that the identity has to be calculated as the number of identical residues in a global alignment of the two sequences over the number of residues of the longer of the two sequences.

Amendments (Article 123(2) EPC) - claims 1 and 9

11. The application discloses in the section "*Preferred aspects*" (spanning pages 89 to 94) a combination of the "preferred aspect" 2 on page 89 ("*2. An isolated polypeptide comprising an amino acid sequence having at least 85%, more preferably at least 90%, even more preferably at least 95%, most preferred 99% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 4.*") with the preferred aspect 1c on page 92 ("*1 c. A pharmaceutical composition comprising the polypeptide of any one of aspects 1 to 11 or a nucleic acid of any one of aspects 1a to 4a and a pharmaceutically acceptable carrier or excipient.*"). The subject-matter of claim 1 differs from this disclosure in the following three aspects:

(i) "immunogenic or vaccine composition"
(ii) "isolated polypeptide ~~comprising an amino acid sequence~~ having at least ... % sequence identity"
(iii) "86% sequence identity"

12. With regard to difference (i), the board notes that immunogenic or vaccine compositions comprising C-TAB.G51 (SEQ ID NO: 4) or its variants are a preferred embodiment of the application (see e.g. paragraphs [0100] and [0155]), and their selection as a preferred pharmaceutical composition thus does not result in added subject-matter.

13. With regard to difference (ii), the board agrees with the respondents that "*the word 'comprising' ... encompasses two possibilities, i.e. 'consists of' or 'containing'*" because "consists of" represents the maximum of what can be "comprised" in a given entity. Considering the wording of claim 1 of the application,

the maximum length of an amino acid sequence which can be comprised in a polypeptide is the whole length of the polypeptide, i.e. the polypeptide consists of the amino acid sequence. The term "consisting of" thus represents an extreme of "comprising" and is thus also implicitly disclosed by it (see also decisions T 107/14, point 1.1; T 725/08, points 5.4 to 5.6 and T 759/10, point 7.1).

14. Further passages referred to by the respondents, e.g. paragraph [0131]: "*vaccine comprising a polypeptide having the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4.*" and paragraph [0187]: "*The C-TAB isolated polypeptides of the present invention may have at least 85%, 86%, [...], or 99% sequence identity or sequence similarity with SEQ ID NO: 2 or SEQ ID NO: 4.*", also directly and unambiguously disclose polypeptides having (in the sense of "consisting of", see point 4. above) the amino acid sequence of SEQ ID NO: 4 or a certain sequence identity to it.

15. With regard to difference (iii), the appellant argued that the subject-matter of claim 1 resulted from the undisclosed combination of features from three lists in paragraph [0187] of the application as filed:

(1) "86%" from the list of "*least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%*" (15 different options)
(2) "sequence identity" from "*sequence identity or sequence similarity*" (two different options)
(3) "SEQ ID NO: 4" from "*SEQ ID NO: 2 or SEQ ID NO: 4*" (two different options)

16. The board does not agree because the skilled person reading the patent application would consider each

combination of a specific sequence identity with a particular sequence (here, 86% sequence identity and SEQ ID NO: 4 in paragraph [0187]) as disclosed (see also decision T 2134/10, point 11: "A *specific degree of sequence identity is not a property that, in combination with a particular molecule selected from Table 1, could single out a particular molecule or confer properties to the claimed subject matter not directly and unambiguously derivable from the application as filed*").

17. Finally, the board notes that specific sequence identities (e.g. 85%, 90%, 95% and 99%), and not similarities, are disclosed in combination with SEQ ID NO: 4 in the "preferred aspect" 2 on page 89 of the application. The skilled person would thus derive directly and unambiguously from the list in paragraph [0187] that those percentage values could be replaced with one specific value (e.g. "86%").

18. Accordingly, claim 1 fulfils the requirements of Article 123(2) EPC.

19. The appellant submitted that claim 9 related to added subject-matter because neither the claims nor paragraph [0119] of the application disclosed the isolated polypeptide being used in the prevention or treatment of a CDAD.

20. The board does not agree and considers that the skilled person would derive the subject-matter of claim 9 directly and unambiguously from the passage "*Accordingly, the invention provides immunogenic compositions useful for the prevention or treatment of C. difficile associated disease in subjects in need thereof*" (see paragraph [0128]) in combination with the

disclosure discussed above for the subject-matter of claim 1.

21. Claim 9 thus also fulfils the requirements of Article 123(2) EPC.

Extension of scope of protection (Article 123(3) EPC) - claim 2

22. This claim (see section II) differs from claim 2 as granted only in the use of the word "and" instead of "or" in the expression "10^2, 10^3 and 10^4 *Clostridium difficile* spores". It therefore requires 100% survival to occur after challenge with all spore doses ("and"), i.e. only peptides which achieve 100% survival of hamsters after challenge with all three doses are covered by the claim. Such peptides are, however, also covered by the "or" language of granted claim 2.

23. Indeed, claim 2 as granted requires that 100% survival can occur at each of the three specified spore doses ("or"), i.e. polypeptides which achieve 100% survival after challenge with the highest dose (10^4) are included, as are polypeptides which achieve 100% survival after challenge with the intermediate (10^3) or the lowest (10^2) dose. Common general knowledge, however, predicts that polypeptides that achieve 100% survival after challenge with the highest dose must also achieve 100% survival after challenge with the medium or with the lowest dose. The "and" combination in the claim is thus implicitly covered by one of the alternatives in granted claim 2 ("after intragastric administration of a dose of ... 10^4 *Clostridium difficile* spores").

24. The claim therefore does not extend the scope of protection provided by the patent.

Novelty (Article 54 EPC) - claim 1

25. In accordance with the interpretation of the wording "isolated polypeptide having at least 86% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 4" (see points 2. to 7. above), the polypeptide having SEQ ID NO: 21 disclosed in document D4 has 85.24% sequence identity to SEQ ID NO: 4 (see document D18). The polypeptide of SEQ ID NO: 6 disclosed in document D1 has 54.54% sequence identity to SEQ ID NO: 4 of the patent (see document D12).

26. The claimed subject-matter is thus novel in view of the disclosure of document D1 (Article 54(2) EPC) and document D4 (Article 54(3) EPC).

Sufficiency of disclosure (Article 83 EPC)

27. It is established case law of the boards that an application may only be objected to for lack of sufficient disclosure if there are serious doubts, substantiated by verifiable facts (see Case Law of the Boards of Appeal of the EPO, 9th edition, 2019, II.C.7.1.4).

28. The appellant alleged that it constituted an undue burden for the skilled person to provide linkers other than those in the examples of the patent which all contained the RSMH four amino acid linker. However, the board finds confirmation in e.g. paragraphs [0066] and [0080]) of the patent that it was common general knowledge in the technical field how to link polypeptides in a fusion protein. Therefore, the mere allegation of the appellant, in the absence of

supporting evidence, cannot question sufficiency of disclosure in this respect.

29. The board also does not agree with the appellant's mere contention that the fact that only a limited number of ways (specific fusion polypeptides) to practice the invention were exemplified in the patent led to a lack of sufficiency of disclosure. In fact, the skilled person, with due regard to the teaching of the patent and the common general knowledge, was able to generate conservative substitutions, delete or add repeats of the toxins A and B (see paragraphs [0040] and [0060] to [0065]), and/or modify the linker (see paragraph [0066]). Starting from the examples disclosed in the patent, which demonstrate an immunogenic - and even protective - effect, the skilled person could generate such variants and test them in a straightforward way for their immunogenicity without undue burden (see guidance for this in the patent, e.g. paragraph [0069]). Moreover, the known variations from different *C. difficile* strains can be combined to arrive at a larger number of variants than when only combining the variations from two strains.

30. The appellant has also referred to the problem of incorrect folding and degradation of related fusion proteins comprising toxin A and B as exemplified by document D3. This general folding problem is, however, recognised in the patent (see paragraph [0015]). So the skilled person, when generating fusion proteins as referred to in the claim, would check and take routine countermeasures if necessary to avoid this issue. Moreover, the fusion protein disclosed in document D3 has a different structure to the one defined in claim 1, comprising about 10 toxin A repeats, about 15 toxin B repeats (as well as a 133 amino acid residue

region from toxin B before the start of the C-terminal repeat domain of toxin B) and the *C. perfringens* enterotoxin. The fusion protein of document D3 thus has only about 40% sequence identity to SEQ ID NO: 4. Problems reported in document D3 with regard to folding and degradation can therefore not raise serious doubts about the suitability of the polypeptides defined in the claims as part of an immunogenic or vaccine composition.

31. The appellant has further alleged that the patent did not sufficiently disclose the medical use for the prevention or treatment of a *C. difficile* associated disease as defined in claim 9 of fusion proteins containing substantial differences compared to SEQ ID NO: 4. The appellant has, however, not substantiated this allegation with facts. Moreover, a medical use (i.e. immunogenic and protective effect) is disclosed for two variants, C-TAB.G5 and C-TAB.G5.1, in the patent, and the board is satisfied that the skilled person starting from this teaching and following the guidance in the patent can generate further variants suitable for a medical use without undue burden.

32. The board concludes from the above that it has not been presented with any evidence that the skilled person would face an undue burden to practice the invention or that the polypeptides as defined in the claim would not have the immunogenic and vaccine properties required by the claim. In contrast, the experiments performed on mice, hamsters and monkeys (Examples 2 to 10) reported in the patent are considered by the board to demonstrate the suitability of the disclosed fusion polypeptides for medical use.

33. In view of the above considerations, the requirements of Article 83 EPC are fulfilled.

Inventive step (Article 56 EPC)
Closest prior art and differences

34. Both parties agreed with the opposition division that the disclosure in document D1 represented the closest prior art for the subject-matter of claim 1. The board sees no reason to deviate.

35. Document D1 discloses immunogenic or vaccine compositions against *Clostridium difficile*, in particular live bacterial vectors expressing *C. difficile* antigens. In one embodiment, it discloses a construct for integration into the *Salmonella* genome which produces a translation fusion of ClyA-toxin A repeats-toxin B repeats with the amino acid sequence SEQ ID NO: 21 (see Figure 5c) that results in "*the recombinant antigens of the invention* [to be] *contained within a bacterial outer membrane vesicle, for instance, a Salmonella outer membrane vesicle*" (see paragraph [0012]), i.e. the polypeptide in the vaccine composition is not isolated. This recombinant polypeptide antigen shares 54.54% sequence identity with the sequence of present SEQ ID NO: 4 over its whole sequence (see document D12). The parties agreed that it differs from the polypeptide of present SEQ ID NO: 4 by the presence of a ClyA secretion leader, a longer toxin A fragment (39 vs 19 repeats) and a different linker region.

Objective technical problem

36. The technical effect resulting from this difference is that the fusion peptide provides neutralising

properties against toxin A and B in an immunogenic or vaccine composition in an isolated form.

37. The board thus agrees with the objective technical problem formulated by the opposition division, namely "*provision of a C. difficile immunogenic composition comprising an isolated polypeptide providing neutralising properties against toxin A and B*".

38. The appellant argued that claims 1 and 9 referred to a large number of isolated polypeptide variants while an immunogenic or protective effect had been shown in the patent only for two polypeptides, C-TAB.G5 and C-TAB.G5.1 (see Examples), which merely differed from each other by two amino acids. The sequence identity of 86% allowed for in the claim meant that variants could differ by as many as 134 amino acids. Since toxin A and B were highly conserved proteins, changes of this degree could disrupt the repeat domain structure and obliterate epitopes required for the immunogenic effect. It could therefore not be expected that each of the fusion proteins referred to in claims 1 and 9 had neutralising activity against toxin A and toxin B. The objective technical problem needed therefore to be less ambitious.

39. Claim 1 defines the composition as "immunogenic or vaccine" and thus any composition not having immunogenic or vaccine activity is excluded from the claimed subject-matter. Claim 9 defines the isolated polypeptide or the composition of claims 1 to 8 to be for use in the prevention or treatment of a *C. difficile* associated disease (CDAD). The question whether the patent enables the skilled person to obtain compositions or isolated polypeptides having the structural and functional features defined in the

claims without undue burden is thus a question of sufficiency of disclosure (see decision G 1/03, OJ EPO 2004, 413, point 2.5.2 of the Reasons: "*If an effect is expressed in a claim, there is lack of sufficient disclosure. Otherwise, ie if the effect is not expressed in a claim but is part of the problem to be solved, there is a problem of inventive step*"), which was answered above (see points 27. to 33.).

Obviousness

40. Although document D1 teaches in paragraphs [0012] and [0088] that "*recombinant antigens*" could be "*isolated*", it does not disclose if and how those "*isolated recombinant antigens*" should be delivered to a human. Paragraph [0090], which refers to a "*formulation of the recombinant antigen as a composition for delivery to a subject, such as oral delivery to a human patient*", states that the "*recombinant antigen may be contained within a bacterial outer membrane vesicle*", thus leaving doubts whether administration of an "*isolated recombinant antigen*" is at all envisaged. Document D1 also cautions in paragraphs [0006] and [0007] that:

"*while the C. difficile toxins are immunogenic in both animals and humans using various immunization routes, successful vaccines have not been generated. For instance, parenteral immunization with the C. difficile toxins generates a systemic anti-toxin response which is only partially protective upon intact C. difficile challenge (Lyerly et al., Gurr. Microbial. 21 :29-32 (1990)). Further, immunization of hamsters with toxin A repeats provides protection from toxin A challenge, but provides only partial protection in the animal model from subsequent challenge with intact C. difficile.*

[007] Accordingly, a vaccine for inducing protective immunity in humans against the gut pathogen C. difficile must present the vaccine antigen to the host immune system in a manner that stimulates effective immune response(s), which likely include mucosal and systemic humeral responses."

41. The preferred vaccine formulation in document D1 is set out in paragraph [0090] ("*The microorganism may be formulated as a composition for delivery to a subject, such as for oral delivery to a human patient*") and in the claims, which all relate to "*attenuated microorganism*", "*recombinant peptide comprising ClyA secretion signal*" or "*polynucleotide encoding the recombinant peptide*", i.e. implying secretion from a host cell.

42. The board thus concludes that although isolated recombinant antigens are disclosed in document D1, the document fails to instruct the skilled person to use such antigens for vaccination. The skilled person aiming to find an immunogenic composition with a neutralising effect against toxin A and B and comprising an isolated polypeptide would thus find no pointer in document D1 to modify the disclosed fusion proteins by deleting the ClyA signal leader sequence. Also, the fact that document D1 discloses that ClyA is potentially harmful to patients because it has haemolytic activity (see paragraph [0045]) is not conducive to motivating the skilled person to remove this sequence as other ways of overcoming this problem by modification of the sequence are equally disclosed (see paragraph [0045]).

43. The fusion protein disclosed in document D1 also has a longer toxin A fragment. To arrive at the claimed

invention, the skilled person - in addition to removing the ClyA sequence - had to remove parts of the toxin A repeats present in the fusion protein according to SEQ ID NO: 21 (i.e. to reduce the repeats from 39 to 19). Document D1 states in paragraph [0085] that "[t]*he recombinant antigens of the invention may, in some embodiments, comprise the toxin A C-terminal repeat region and/or the Toxin B C-terminal repeat region, where each comprise at least about 5 repeat units, or at least about 15 repeat units. For example, the immunogenic portion of the toxin A C-terminal repeat region may comprise at least about 20 or 25 repeat units, such as about 28 repeat units. The immunogenic portion of the toxin B C-terminal repeat region may comprise at least about 15 repeats, such as about 17 repeats*". The examples of document D1, however, only relate to fusion proteins having 39 toxin A repeats and 23 toxin B repeats.

44. The examples describe in more detail the construction of *Salmonella* vectors (e.g. ZS121 comprising the construct for expression of SEQ ID NO: 21, "FusionAB") and report the presence of mRNA related to the antigenic constructs (see page 31, Table 2). Document D1 is, however, silent on whether the construct of SEQ ID NO: 21 yielded a properly folded and secreted protein product when expressed in the attenuated *S. typhi* vector, or whether a deletion of the ClyA signal leader had any detrimental effect on expression and/or folding and what effect the deletion of repeats from toxin A has on expression, folding and immunogenicity of the fusion protein.

45. In view of the above considerations, the subject-matter of claim 1 is not obvious to the skilled person having regard to the disclosure in document D1 alone.

46. Document D6 (similar to document D1) relates to surface display or secretion of peptides from live attenuated bacteria. It discloses expression constructs of separate toxin A and toxin B fragments with a ClyA secretion signal. One of the disclosed peptides is 14CBD/A, which has 14 repeats of toxin A (see Figure 1 and page 12, lines 20 to 28). Document D6, however, is silent on any immunogenic effect of this truncated toxin A fragment (see hypothetical Examples 6 to 8).

47. Document D3 discloses a recombinant fusion protein comprising toxin A and B fragments and reports an immunogenic effect in mice (see Table 2). However, this fusion protein contains a further component (*C. perfringens* enterotoxin) and a different number of toxin A and toxin B repeats (10 and 15, respectively) compared to the fusion protein of claim 1, i.e. the sequence is only about 40% identical to SEQ ID NO: 4.

48. Thus, when starting from the construct disclosed in document D1 (see point 35.) and aiming to provide an "*immunogenic composition comprising an isolated polypeptide providing neutralising properties against toxin A and B*" (see point 37.), the skilled person would not derive any guidance from documents D6 or D3 that a construct as referred to in the claims (i.e. having 19 toxin A and 23 toxin B repeats and lacking the *C. perfringens* enterotoxin) would be a solution.

49. The board thus concludes that the subject-matter of claim 1 is not obvious to the skilled person also having regard to the disclosure of documents D6 or D3.

50. The subject-matter of claim 1 thus involves an inventive step. The same applies to the remaining

claims, which all refer to claim 1 or concern the same immunogenic isolated polypeptide of claim 1.

Reimbursement of the appeal fee

51. The respondents withdrew their appeal before the decision was announced at oral proceedings (see section XI.). As a consequence, the appeal fee is to be reimbursed at 25% in accordance with Rule 103(4)(a) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

I. Aperribay B. Claes

Decision electronically authenticated