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D E C I S I O N
of 5 April 2006

Case Number: T 0293/04 - 3.3.08

Application Number: 92111713.1

Publication Number: 0522560

IPC: C12N 15/31

Language of the proceedings: EN

Title of invention:

Method and composition for the prevention of Lyme disease

Patentee:

Baxter Aktiengesellschaft

Opponent:

MIKROGEN molekularbiologische Entwicklungs-GmbH

Headword:

Lyme vaccine/BAXTER

Relevant legal provisions:

EPC Art. 87, 54, 56, 83

Keyword:

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

Decisions cited:

G 0002/98, T 0890/02, T 1329/04

Catchword:

-



Case Number: T 0293/04 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 5 April 2006

Appellant:
(Patent Proprietor)

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Decision under appeal:

Decision of the Opposition Division of the
European Patent Office posted 22 December 2003
revoking European patent No. 0522560 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: T. J. H. Mennessier
Members: P. Julià
C. Rennie-Smith

Summary of Facts and Submissions

- I. European patent No. 0 522 560 with the title "Method and composition for the prevention of Lyme disease" was granted on the basis of European patent application No. 92 111 713.1 and claiming priority from applications US 727245 (filed on 11 July 1991), US 824161 (filed on 22 January 1992) and US 903580 (filed on 25 June 1992).
- II. An opposition had been filed under Articles 100(a), (b) and (c) EPC. The patent was revoked by the opposition division on the grounds that the main request and the first auxiliary request for all designated Contracting States except Spain (ES) filed on 8 March 2002 did not fulfil the requirements of Article 56 EPC.
- III. The patentee (appellant) filed a notice of appeal and paid the appeal fee. With the statement of grounds of appeal of 19 April 2004, two sets of claims, one for all the designated Contracting States except ES and the other for ES, were filed, each consisting of a main request and a first auxiliary request. The requests for all Contracting States except ES were identical to the requests on which the decision under appeal was based.
- IV. Observations were filed by the opponent (respondent) in its letter of 19 August 2004 in reply to the statement setting out the grounds of appeal. In turn, the appellant filed on 15 February 2005 additional comments in reply to those observations.
- V. On 19 January 2006, accompanying the summons to the oral proceedings, a communication was sent to the

parties pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal (RPBA) (OJ EPO, 2003, 89), wherein the board expressed some provisional and non-binding opinions.

VI. On 2 March 2006, the respondent replied to the board's communication and submitted two further documents.

VII. For reasons unknown to the board, the respondent's letter and its enclosures were not passed to the board promptly after delivery to the EPO. The appellant was informed of the respondent's letter only on 29 March 2006. In its letter of 30 March 2006, the appellant requested that the oral proceedings be postponed.

VIII. The board considered that a postponement of the oral proceedings was disproportionate to the inconvenience caused by the late filing and delayed transmission of the respondent's submissions to the appellant and the request for postponement was refused on 30 March 2006.

IX. Oral proceedings took place on 5 April 2006 as scheduled.

X. Claim 1 of the main request for all designated Contracting States except ES read as follows:

"1. A vaccine against Lyme borrelioses, characterized by comprising an immunogen which is a mixture of different serological forms of non-denaturated B. burgdorferi pC polypeptide in an amount effective to immunize a susceptible mammal against Lyme borreliosis, wherein said amount is in the range of 1 to 100 µg per immunogen per dose and an adjuvant."

Claims 2 to 9 were dependent on claim 1 and directed to particular embodiments thereof. Claim 7 referred to the pC polypeptide as being a recombinant polypeptide produced in transformed host cells. Claim 8 defined the pC polypeptide as comprising an amino acid sequence that was encoded by a DNA sequence amplifiable by polymerase chain reaction with a specific oligonucleotide primer pair indicated in the claim.

XI. The following documents are mentioned in the present decision:

P1: US 727,245 (filing date: 11 July 1991), first priority document of the patent in suit;

D2: DE-C1-39 42 728 (publication date: 23 May 1991);

D3: WO-A-91/09870 (publication date: 11 July 1991);

D6: EP-A1-0 418 827 (publication date: 27 March 1991);

Annex C: B. Wilske et al., Annals of the New York Academy of Sciences, 1988, Vol. 539, pages 126 to 143.

XII. The appellant's arguments, made in writing and during the oral proceedings, insofar as they are relevant to the present decision, may be summarized as follows:

Article 87 EPC; priority

A deposit of the *Borrelia burgdorferi* strain Orth-1 was only necessary if document P1 failed to provide enough

information for the skilled person to isolate the pC polypeptide from other *B. burgdorferi* strains. This was not the case since document P1 provided a method for purifying the pC polypeptide that could be successfully applied to other *B. burgdorferi* strains, such as those described in document Annex C. This latter document demonstrated that a large percentage of North American *B. burgdorferi* isolates expressed the pC polypeptide. Evidence was on file showing that this percentage was understated and that a higher percentage of strains expressed the pC polypeptide. The possible presence of other proteins with molecular weights similar to the pC polypeptide was not supported. In any case, there was evidence on file showing that the identification of the pC polypeptide by SDS-PAGE was reliable and reproducible. Thus, the identification of *B. burgdorferi* strains producing pC polypeptide and the isolation of this polypeptide did not place an undue burden on the skilled person and the deposit of the *B. burgdorferi* strain Orth-1 was not necessary.

Document Annex C further demonstrated that serotyping techniques were known and available to the skilled person. These techniques allowed identification of isolates of *B. burgdorferi* expressing different serological forms of the pC polypeptide. The selection of *B. burgdorferi* strains, the isolation of different serological forms of the pC polypeptide from those isolates and the provision of a mixture of serological forms for producing a vaccine did not place an undue burden on the skilled person.

The teachings of document P1 were supported by the examples. Example 1 described in detail a method of

purification that allowed isolation of a non-denaturated (homogeneous) pC polypeptide from *B. burgdorferi*. The SDS-PAGE and immunoblotting of Example 2 merely demonstrated the purity of the antigens isolated from the chromatographic fractions. These assays, which did not require the use of the whole chromatographic fraction, only showed the presence and purity of the desired antigen. Example 3 showed the immunogenic properties of the isolated non-denaturated pC polypeptides. These examples demonstrated that homogeneous, non-denaturated pC polypeptides from different *B. burgdorferi* strains could be purified by the method of Example 1 and used in the preparation of a vaccine as taught in document P1.

Article 54 EPC; novelty

None of the documents on file disclosed the features of the claimed subject-matter. Document D2 did not provide a mixture of serological forms of pC but a combination of different antigens (p41, pC and p17). The production of recombinant proteins referred to in document D2 was intended only for obtaining pure antigens and there was no indication that these recombinant antigens had to be in non-denaturated forms, let alone that these forms could be used as vaccines.

Since the patent in suit enjoyed a right of priority from the first priority document, document D3 was prior art pursuant to Article 54(3) EPC. According to the established case law, the combination of different parts of one document was permissible only if a person skilled in the art would acknowledge that they were

clearly connected. The parts of document D3 containing references to two different serological pC forms were not so connected and there was no suggestion that these forms (with agents stimulating an immune response) should be combined.

Article 56 EPC; inventive step

Three features differentiated the claimed vaccine from the prior art: i) the selection of pC as specific antigen, ii) the use of different serological pC forms, and iii) the fact that these forms were non-denatured. None of these features was suggested in the prior art, let alone a combination thereof. In comparison with the prior art, in particular with documents D2 and D6, the patent demonstrated that pC was actually capable of producing a protective immune response.

Whereas document D6 was not even concerned with the pC protein, document D2 referred to this protein among several other immunologic active proteins of *B. burgdorferi*. Although the use of all these proteins for the production of a vaccine against *B. burgdorferi* was mentioned, there was no suggestion of choosing the specific pC protein nor any indication that this protein could actually be useful in a vaccine.

Starting from the closest prior art, the technical problem underlying the patent in suit was the provision of an effective vaccine against the Lyme borreliosis in mammals. The patent solved the problem by providing a vaccine comprising a mixture of non-denatured serological forms of the pC polypeptide.

It was well-known that not all immunogenic antigens produced a protective immune response. Protective antigens were relatively rare and numerous factors were important for evaluating whether an antigen could be used as a vaccine. In particular, a model system (in the present case mimicking Lyme disease in humans) had to be chosen so as to assay the desired protective immune response and the dosage of the immunologic active protein. None of these factors was addressed in document D2. The skilled person, being conservative and unwilling to take risks, would not have relied on a vague indication in the prior art if there was no technical substantiation and a large amount of research work still to be done. This was the case in document D2 with regard to the use of the pC polypeptide in a vaccine. There was no hint leading the skilled person to select the pC polypeptide nor any indication to combine this polypeptide with the two other features of the claimed subject-matter, i.e. different serological forms in a non-denaturated conformation. These features could only be achieved with hindsight.

The patent provided a method for purifying the pC polypeptide in a non-denaturated conformation, i.e. as close as possible to its original or native conformation, which was advantageous vis-à-vis the partially non-denaturated pC polypeptide available in the prior art. The use of different serological forms advantageously allowed a broader range of infectious agents to be covered. The combination of these two features (serological forms in non-denaturated conformation) contributed to the inventive step and they were not derivable from any of the prior art documents on file, particularly document D2. The

decision under appeal relied only on a rather amorphous statement with regard to the "general knowledge" in the art. However, there was no evidence on file supporting this "general knowledge".

The present situation was different from that in decision T 1329/04 of 28 June 2005, which was concerned with a patent application in which no actual technical information was provided. In the present case, the patent was technically supported. Example 3 demonstrated that a non-denaturated pC polypeptide produced an advantageous protective immune response in comparison with other antigens from *B. burgdorferi*. It was also plausible that this result could be obtained with a mixture of non-denaturated, serological pC forms. There was no evidence on file undermining the teachings of the patent in suit.

Article 83 EPC; sufficiency of disclosure

As with the priority document P1, in the light of the teachings of the patent in suit (a non-denaturing method of purification) and the general knowledge of the presence of *Borrelia* serotypes, and more particularly, of the presence of serological forms of the pC polypeptide, the skilled person had encountered no undue difficulties in achieving a vaccine comprising a mixture of non-denaturated, serological forms of the pC polypeptide. There was no evidence on file showing that a vaccine such as that claimed was not effective.

Adaptation of the description

The examples shown in the patent in suit were in line with the general disclosure and, more particularly, with the description adapted to the request under consideration.

- XIII. The respondent's arguments, made in writing and during the oral proceedings, insofar as they are relevant to the present decision, may be summarized as follows:

Article 87 EPC; priority

According to the established case law (cf. G 2/98, OJ EPO 2001, 413), a priority right was to be acknowledged only if the skilled person could derive the claimed subject-matter directly and unambiguously, using common general knowledge, from the previous application as a whole. Moreover, the priority document had to be enabling and to disclose all the essential elements of the invention. Missing elements which were only recognized later as essential were not part of the disclosure, i.e. the desired result had to be achieved without undue burden and without exercising any inventive skill.

The *B. burgdorferi* strain Orth-1 had not been deposited and, thus, a pC polypeptide was not available to the skilled person. In order to repeat the teachings of document P1, it was necessary to identify *B. burgdorferi* strains that expressed a pC polypeptide, purify the pC polypeptides from these strains and select different serological forms of these polypeptides. According to the document Annex C, only

40 to 50% of the *B. burgdorferi* strains expressed a pC polypeptide. However, this expression was not constitutive but dependent on the conditions of culture. The *B. burgdorferi* strain PKo mentioned in the document Annex C and in documents D2 and D3 had a constitutive expression of pC polypeptide caused by a mutation, which was not found, however, in other *B. burgdorferi* strains. Thus, the identification and selection of strains expressing the pC polypeptide was not straightforward.

Moreover, several proteins with a molecular weight in the range of 21-22 kDa similar to that of the pC polypeptide were normally expressed by *B. burgdorferi*. The amount and number of those proteins could also be different depending on the particular *B. burgdorferi* strain considered. There was no indication in document P1 as to how the pC polypeptide could be differentiated from these other proteins and, due to its denaturing character, the SDS-PAGE technique of document P1 could not be used for isolating the pC polypeptide. The purification and provision of a mixture of different serological forms of homogeneous, non-denatured pC polypeptide for the production of a vaccine placed an undue burden on the skilled person.

Although serotyping methods were known, they could produce very different results. Document P1 failed to disclose which method had to be used for serotyping the pC polypeptides and which criteria (amount and type of cross-reactivity) defined a serological pC form. In the absence of such information, the teachings of document P1 were not reproducible. Document P1 did not disclose a recombinant pC polypeptide nor the essential elements

(the specific primer pair mentioned in the claims) required for its production.

In conclusion, since document P1 did not contain any example of a vaccine comprising a mixture of different non-denaturated, serological forms of *B. burgdorferi* pC polypeptide and it failed to disclose and to provide the essential elements for carrying out the invention, it did not enable the skilled person to achieve the claimed subject-matter without undue effort. Thus, a right of priority based on document P1 could not be acknowledged.

Article 54 EPC; novelty

According to the established case law, the same standard had to be used when comparing the disclosure of the contested patent with the prior art. Since the patent did not disclose a mixture of non-denaturated serological forms of the pC polypeptide, this feature could not differentiate the patent from the prior art. Evidence was on file showing that it was common general knowledge that for a vaccine it was advantageous to have the antigen in a non-denaturated conformation.

Document D2 disclosed a recombinant (non-denaturated) pC polypeptide for use in a vaccine. The actual technical disclosure of this document was identical to that of the patent in suit. The application on which this patent was granted was the basis for claiming the earliest priority of document D3, which disclosed two serological forms of the pC polypeptide derived from *B. burgdorferi* strains PKo and ATCC 35210. These forms had a molecular weight of about 22 kDa and differed in

their amino acid sequences. The use, alone or in combination, of the disclosed proteins as antigens for induction of an immune response was contemplated in document D3, which explicitly identified the pC polypeptide as a preferred antigen. Document D3 further referred to the isolation of the pC polypeptide from different strains of *B. burgdorferi* and to the production of recombinant (native, non-denaturated) pC polypeptide. The use of denaturing agents in some steps of the purification method could result in a temporary denaturation of the polypeptide, which was, however, easily reverted to the non-denaturated form by standard methods, such as the dialysis mentioned in document D3. The other features referred to in the claims of the patent in suit also lay within the common general knowledge of the skilled person. Thus, document D3 anticipated the claimed subject-matter.

Article 56 EPC; inventive step

The demonstration of an effect (use of the pC polypeptide as a vaccine) that was already indicated in the prior art (document D2) could not amount to an inventive step. The presence of serological forms (antigenic variability) of the pC polypeptide was shown in document D3. It was also known from earlier prior art, such as document Annex C. Therefore, although not exemplified therein (nor was it in the patent in suit), the use of these serological pC forms for a vaccine was obvious. It was also known that for a vaccine, the immunogen had to be as close as possible to the native antigen. In fact, that was an inherent feature of an immunogen for use in a vaccine. Therefore, it was normal routine to develop methods of purification for

non-denatured immunogens, such as the standard recombinant methods. The use of those non-denatured immunogens for vaccines was a normal practice in the field as supported by evidence on file.

Document D6 disclosed recombinant OspA and OspB polypeptides and their use, alone or in combination with other antigens from *B. burgdorferi*, as vaccines. These recombinant polypeptides had a native (non-denatured) conformation. Documents D2 and D3 disclosed the use of the polypeptide pC in a vaccine, the latter document disclosing two serological forms of this polypeptide, known from the prior art (document Annex C) to have antigenic variability. The combination of this prior art led the skilled person to the claimed subject-matter in an obvious manner.

The patent in suit comprised a single example which showed the protective effect of a vaccine containing a pC polypeptide. However, a mixture as in claim 1 had not been exemplified and there was no evidence on file demonstrating that a vaccine comprising such a mixture provided a protective immune response let alone an improved one over the vaccines known in the prior art. The patent failed to show that the proposed (obvious) solution actually worked and that the problem it purported to solve vis-à-vis the prior art had been credibly solved. This situation was similar to that underlying decision T 1329/04 of 28 June 2005, which stated that the mere formulation of a technical problem was no basis for establishing inventive step and that post-published evidence could not serve as the sole basis to establish that the application did in fact solve the problem it purported to solve. Moreover, it

was also established case law that where, as in the patent in suit, the only example was described as a hypothetical experiment, then the burden of proof was on the patentee to show that what was described actually worked.

Article 83 EPC; sufficiency of disclosure

As with the priority document P1, the actual disclosure of the patent in suit was restricted to a mere suggestion of a possible use of a mixture of (non-denaturated) serological forms of the pC polypeptide in a vaccine against *B. burgdorferi*. This suggestion, however, was not supported by any technical data. The patent in suit disclosed only a single serological form of the pC polypeptide. As argued for the priority document P1, there was no evidence in the patent in suit that a mixture of those serological forms was effective in a vaccine nor that such a mixture represented an improvement over known vaccines comprising a single serological pC form.

Adaptation of the description

Since none of the examples of the patent disclosed the mixture of the claimed vaccine let alone data on the immune protective effect of such a vaccine, examples of the patent had to be cited as "reference examples" only and not as exemplifying the claimed subject-matter.

- XIV. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request for all designated Contracting States except ES filed with the

statement of grounds of appeal, the claims of the main request for the designated Contracting State ES and pages 3 to 5, 7 and 8 of the description, both as filed at the oral proceedings, page 2, 6 and 9 to 13 of the description as granted, and the two figures as granted.

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

Reasons for the Decision

Main request for all the designated Contracting States except ES

Article 87 EPC; priority

1. The technical features characterizing the subject-matter of claim 1, in particular "*a mixture of different serological forms of non-denaturated B. burgdorferi pC polypeptide*", have a formal basis in the priority document P1. References to the features of dependent claims 2 to 7 are also found in this document, including recombinant methods for producing serological forms of the pC polypeptide.

2. According to the established case law, a priority document must disclose the invention as a matter of substance, i.e. it must contain an enabling disclosure with all the essential features so that a skilled person can carry it out without undue burden or inventive skill (cf. "Case Law of the Boards of Appeal of the EPO", 4th edition 2001, IV.B.1.3, 238 and IV.B.3, 242). Since the *B. burgdorferi* strain Orth-1 of

- document P1 had not been deposited and there was no example in this document of a vaccine comprising a mixture as defined in claim 1, the question arises as to whether all the elements necessary to perform the invention, in particular the serological forms of the non-denaturated pC polypeptide, were available to the skilled person at the earliest priority date.
3. Document P1 discloses a non-denaturing method of purification (cf. page 20, line 19 to page 24, line 4) which, although exemplified with antigens of the *B. burgdorferi* strain Orth-1 (cf. Examples 1 and 2, pages 25 and 28, respectively), is not limited to this strain but intends to be of general applicability for purifying *B. burgdorferi* proteins (cf. *inter alia* page 6, lines 23 to 25 and page 7, line 23 to page 8, line 10).
 4. Evidence is on file showing that, at the earliest priority date, no difficulties would have been encountered in identifying *B. burgdorferi* strains expressing the pC polypeptide, which could then be isolated using the non-denaturing method of document P1. Document Annex C discloses such identification by SDS-PAGE (cf. Figure 1, page 130) - as done in document P1 for the fractions of the purification method and the purified pC polypeptide (cf. Figure 1 of document P1) - and by using an antibody raised against the pC polypeptide of *B. burgdorferi* strain PKo (cf. page 129, first full paragraph and Figure 5 on page 133). The specific PKo strain had been deposited and was available to the skilled person (cf. page 3, lines 60 to 63 in document D2). Document P1 explicitly referred to document Annex C (cf. page 2, line 23 to page 3,

line 2 and page 4, lines 10 to 17) and further disclosed a partial amino acid sequence of the pC polypeptide from strain Orth-1 that could be used for raising anti-pC antibodies. Document D2 provides a partial sequence of the pC polypeptide from strain PKO that could also be used for the same purpose (cf. page 9, lines 24 to 25). These sequences are easily identified in the full-length sequence of the pC polypeptide derived from a third *B. burgdorferi* strain (ATCC 35210) too (cf. page 36 of document D3).

5. Document Annex C also shows that, with the means available to the skilled person at the earliest priority date, it was already possible to identify the presence of serological variability for the pC polypeptide (cf. page 135, first full paragraph and page 140, last paragraph). Document D2 also refers to the presence of antigenic variability for the p100 protein (cf. page 6, lines 24 to 25). In fact, methods and criteria for identifying serological variants were standard and well-known to the skilled person. Document P1 itself explicitly referred to prior art disclosing differences in the molecular weight and in the serological reactivity of the outer surface proteins OspA and OspB of *B. burgdorferi* (cf. page 2, lines 7 to 22). No particular difficulties are associated with these serotyping methods.
6. Therefore, at the earliest priority date the skilled person was in a position to achieve without undue burden a vaccine comprising a mixture of different serological forms of non-denaturated *B. burgdorferi* pC polypeptide, i.e. the subject-matter of claims 1 to 6, which are thus entitled to the earliest priority date.

7. *A contrario*, on the basis of the information given in document P1, the claimed earliest priority date cannot be acknowledged for the subject-matter of claim 7 concerning a recombinant pC polypeptide. Nor is a basis for claim 8 relating to a specific oligonucleotide primer pair. Thus, claims 7 to 8 and 9 (which is dependent on claims 7 and 8) are not entitled to the claimed earliest priority date.

Article 54 EPC; novelty

8. According to the established case law, for an invention to lack novelty its subject-matter must be directly derivable from the prior art and it is not acceptable to decide that a document is prejudicial to novelty as a matter of probability (cf. "Case Law", *supra*, I.C.2.1, 54 et seq.).
9. Document D3 is state of the art pursuant to Article 54(3), (4) EPC for those claims entitled to the earliest priority date (claims 1 to 6) and to Article 54(2) EPC for those claims not entitled to this priority date (claims 7 to 9). This document discloses the amino acid sequences of the pC polypeptides from two *B. burgdorferi* strains, namely strains PKo (DSM 5662) (cf. page 7, first paragraph and pages 26 to 27) and ATCC 35210 (cf. example 7, pages 35 to 36). Although both sequences are different, no comments are made on the significance of these differences. The document is also silent on the possible relevance of the detected great variation of p100 from different *B. burgdorferi* strains (cf. page 16, second paragraph). Notwithstanding the fact that the isolation of those

preferred proteins of 22 kD (pC) and 100 kD (p100) from different strains is contemplated (cf. page 13, last but one paragraph), there is no detailed interpretation or further elaboration on the importance of the presence of serological variants for those proteins.

10. References to the use of the disclosed antigens "*alone or in combination*" in a vaccine (cf. paragraph bridging pages 12 and 13) must be interpreted in the context of document D3 as a whole. This document refers as a preferred embodiment to the combined application of the disclosed immunologic active proteins, in particular a combination of the proteins p41, pC, p17 and/or p100 (cf. page 10, second paragraph). It is this very specific combination of four immunologic active proteins which is described as allowing an almost complete coverage of all positive sera and a correlation to the stage of the disease (cf. page 17, end of first paragraph). However, there is no indication whatsoever of a combination comprising the very same immunologic active protein derived from different strains, i.e. a mixture of serological forms.

11. Test kits comprising two to four immunologic proteins in a (recombinant) pure form are also contemplated in document D3 (cf. *inter alia* page 9, first paragraph). Claim 14 relates to those test kits comprising at least one immunologic active protein according to claims 1 to 13. Whereas claim 7 refers to a generic immunologic active protein of 22 kDa (pC), only the amino acid sequence of the pC polypeptide derived from the *B. burgdorferi* strain PKo is given in claim 8 but not the sequence derived from strain ATCC 35210. Thus, a combination comprising these two pC polypeptides is not

directly derivable from these claims. Moreover, the expression "at least one" of claim 14 is not found in claim 22 which is concerned with the use of those immunologic active proteins in the production of a vaccine.

12. The board further fails to see any reference to non-denaturated *B. burgdorferi* antigens in document D3. The use of recombinant methods for producing these antigens does not directly result in non-denaturated products since certain conditions must be maintained to preserve this conformation, such as for instance to avoid the aggregation of the expression products (cf. paragraphs [0040] and [0041] of the patent in suit). The extraction of the membrane fraction may also require the use of non-denaturing agents which must be compatible with further chromatographic steps of the purification method (cf. paragraph [0055] of the patent).

13. In fact, in the first steps of the purification of the intracellular p41 described in document D3, the mild detergents Triton-X-100 and octyl-gluco-pyranoside are used. However, a solubilisation buffer comprising highly denaturant 8 M urea is used before the first chromatographic step (cf. Example 4(a), page 29, last paragraph). Whereas for the pC polypeptide only Triton-X-100 is used (cf. Example 4(b), page 30, second paragraph), a buffer with 2 M urea is referred to in the purification of OspA (cf. Example 4(c), page 31, third paragraph). None of those methods contemplates the use of a non-denaturing agent in the chromatographic steps or in the resulting final product so as to preserve a non-denaturated conformation of the

- purified antigens. Thus, the relevance of maintaining the purified antigens in a non-denaturated conformation is not derivable from these teachings.
14. It follows from the above that none of the two features characterizing the subject-matter of claim 1, namely "*a mixture of different serological forms*" in a "*non-denaturated*" conformation, is directly derivable from document D3. Although the former feature is not exemplified in the patent in suit, it nevertheless imposes some technical constraints on the claimed subject-matter and, thus, it has to be taken into account in the assessment of this subject-matter and of the prior art.
15. The same conclusion is reached considering document D2, which is a prior art pursuant to Article 54(2) EPC for the whole claimed subject-matter, and which was granted on an application that corresponds to the earliest priority document of document D3. The disclosure of this document is less complete than that of document D3, since there is no mention of the two variants of the pC polypeptide nor of any method of purification for this pC polypeptide. No other prior art is on file that anticipates the subject-matter of claim 1.
16. Thus, the requirements of Article 54 EPC are fulfilled.

Article 56 EPC; inventive step

Claims 1 to 6 (entitled to the earliest priority date)

17. Documents D2 and D6 have been cited as possible closest prior art, the latter in the decision under appeal. Therefore, it must first be established which of those

documents represents the closest prior art. Both documents refer to vaccines against Lyme borreliosis comprising immunologic active proteins from *B. burgdorferi*. However, whereas document D6 is mainly concerned with the outer surface proteins OspA and OspB and there is no reference therein to the pC polypeptide, document D2 refers to several immunogenic active proteins (p41, p17 and p100) and explicitly to the pC polypeptide. Thus, document D2 is considered as the more appropriate starting point for the problem-solution approach.

18. Document D2 characterizes four *B. burgdorferi* proteins as immunodominant antigens, namely p17, pC, p41 and p100 (cf. page 6, lines 24 to 25), of which p41 and pC are particularly common in sera from fresh infection cases (cf. page 6, lines 31 to 35). These proteins, alone or in combination, are used in diagnostic test kits and vaccines (cf. *inter alia* page 4, lines 27 to 60 and page 5, lines 36 to 40 as well as claims 9 to 16 and claim 17) and the advantages of recombinant methods for their production are also acknowledged (cf. Examples 2 and 3 for the production of recombinant p41, pC and p100 and example 4 for a method of purification of recombinant p41 protein). These three immunodominant proteins - p41, pC and p100 - are also used for immunization of mice and production of monoclonal antibodies (cf. Example 6).

19. The patent in suit differs from document D2 in that the immunogen used in the production of the vaccine against Lyme borreliosis is a mixture of different serological forms of non-denaturated pC polypeptide from *B. burgdorferi* in an effective amount to immunize a

susceptible mammal (within the range of 1 to 100 µg per immunogen per dose and an adjuvant). No data on the actual results obtained with such a vaccine are provided by the patent and there is no comparison between this vaccine and the possible structurally closest vaccine derived from document D2, i.e. a vaccine comprising the pC polypeptide as immunogen. In this context, it is also noted that document D2 does not provide any data on a vaccine comprising the pC polypeptide as immunogen.

20. Starting from this closest prior art, the technical problem underlying the patent may be described as the provision of an alternative vaccine against Lyme borreliosis. The solution to that problem is a vaccine according to claim 1. Example 3 of the patent shows that the pC polypeptide has a protective effect (cf. Tables 1 and 2 and page 10, from line 55 to page 12, line 14). On this basis in the board's judgment the afore mentioned technical problem is satisfactorily solved.

21. It has been argued that on this basis alone the technical problem cannot be seen as solved (cf. Section XIII *supra*). However, no evidence has been provided in support of this allegation nor is there any indication in the prior art on file that could support it. On the contrary, the production of multivalent vaccines with several structurally unrelated antigens (and the advantages associated therewith) were normally contemplated in the prior art and no particular technical problems were expected to be encountered (cf. *inter alia* page 5, lines 38 to 39 in document D2, claim 24 in document D6). In the absence of any

evidence, there is no reason to expect that those problems would be encountered using more structurally related antigens, such as the serological forms of the patent in suit. Thus, the present situation is different from that underlying decision T 1329/04 (*supra*) as to the quality of evidence provided in the patent in suit relating to the claimed invention being a *bona fide* solution to the problem to be solved.

22. The question to be answered is whether the features characterizing the claimed subject-matter are derived in an obvious manner from the prior art.

Whereas evidence is on file (and it has not been contested) showing that this is the case for the defined immunogen range and the selected adjuvant, the immunogen being a mixture of **serological forms** of the pC polypeptide and the fact that those forms are in a **non-denaturated** conformation remain contentious matter. Moreover, these two features are found in combination in claim 1 and, thus, they must also be considered together in the assessment of inventive step. The specific claimed mixture must be derivable from the prior art in an obvious manner and it must be singled out among other possible mixtures.

The feature "a mixture of serological forms of B. burgdorferi pC polypeptide"

23. Document Annex C discloses antibodies against the pC protein of strain PKo (cf. page 129, Table 3 and first full paragraph) and refers to immunological analysis of different *B. burgdorferi* isolates (cf. *inter alia* Figures 5 and 7, pages 133 and 135, respectively) that

indicate the presence of "*antigenic heterogeneity of the three major variable proteins (OspA, OspB, and pC)*" (cf. page 135, first full paragraph and page 140, last paragraph). However, there is no comment on the relative importance and possible differences of this heterogeneity in relation to each one of these three major proteins. Nor does the document further elaborate on the relevance of this antigenic heterogeneity for the production of a vaccine.

24. Document D2 explicitly cites document Annex C but only in the context of the identification of *B. burgdorferi* by immunologic methods (cf. page 10, lines 60 to 62) and there is no reference to the relevance of the serological heterogeneity. Although document D2 points out that different results are obtained in immunologic tests when using different *B. burgdorferi* strains and that differences are also detected in the expression of the immunodominant pC polypeptide among different *B. burgdorferi* strains (cf. page 3, lines 23 to 27 and 65 to 67), there is no reference to the presence of any heterogeneity for the pC polypeptide. Moreover, the references to the use of two to four active proteins in detection tests and to the possible combination of these antigens for the production of a vaccine (cf. page 4, lines 36 to 37 and page 5, lines 36 to 39) can only be understood - in the context of document D2 as a whole - as being combinations of different active proteins or antigens (p41, pC, p17 and/or p100) but not of different serological forms of these antigens (cf. *inter alia* page 4, line 58 and point 10 *supra*).

The feature "non-denaturated B. burgdorferi pC polypeptide"

25. The preparation of a pure or homogeneous protein in a non-denaturated conformation requires a method of purification that maintains this conformation during all the steps of the method and/or allows the recovery of this conformation at the final steps of the method. In any case, certain conditions (temperature, pH, etc.) and reagents (strong detergents, chaotropic agents, etc.) are to be avoided and appropriate precautions are to be taken so as to prevent irreversible (partial or total) denaturation of the protein, particularly for membrane proteins. These specific conditions and precautions might also involve additional efforts from the skilled person. None of these conditions and precautions is mentioned or indicated in the prior art on file.
26. Document D6 refers to the purification of the recombinant proteins OspA and OspB from *B. burgdorferi* strain ZS7. Example 3 discloses the use of a mild non-denaturing detergent (Triton X-100) after cell lysis. However, a strong denaturing agent (8 M urea) is used for further solubilisation of the precipitated antigen (cf. page 9, lines 35 to 55). Butanol and chloroform are used in the purification of native (non-recombinant) OspA (cf. Example 5, page 13 lines 21 to 32). Although both native and recombinant OspA proteins induce a comparable immune response (which in view of the different methods of purification used - different glycosylation, contaminants, etc. - is in itself not obvious) (cf. page 3, lines 36 to 40), document D6 does not disclose whether, under the

conditions used, these proteins have a native conformation or a (total or partial) non-denaturated one.

27. Nor is there any hint of the importance of a non-denaturated conformation in the closest prior art document D2, which also discloses the use of 8 M urea in the purification of the recombinant intracellular protein p41 (cf. Example 4, page 9, line 49). No method of purification is indicated for the pC polypeptide or for any other (outer surface) membrane protein and there is no indication that for those proteins with a different cellular location particular steps and/or reagents might be required. On the contrary, the method exemplified for the intracellular protein is referred to as being a preferred method for purifying immunologic active proteins in general (cf. page 4, lines 11 to 18).

Common general knowledge

28. It has also been argued that the use of serological forms in a non-denaturated conformation is the normal practice and well within the common general knowledge of the person skilled in the field of vaccines (cf. point XIII *supra* and point 3.3.3.3, page 7 of the decision under appeal). However, this assertion has not been properly supported by any evidence. It is nevertheless established case law of the Boards of Appeal that substantiation of an allegation that something is common general knowledge is required when this is challenged by a party (cf. "Case Law", *supra*, I.D.5.3, 114 et seq.). The type of documents representing the common general knowledge is defined in

the case law, namely encyclopaedias, handbooks, textbooks and general technical literature (cf. "Case Law", *supra*, II.A.2(a), 145 et seq. and *inter alia* T 890/02, OJ EPO, 2005, 497). None of the documents on file nor the documents filed by the respondent after the board's communication under Article 11(1) RPBA (cf. point VI *supra*), and cited in support of the alleged common general knowledge, fall within this definition. Nor do the cited documents refer to a mixture of serological forms.

29. It follows from the above considerations that none of the two features characterizing the claimed subject-matter, i.e. a mixture of serological forms of the pC polypeptide in a non-denaturated conformation, let alone their specific combination, can be derived from the prior art on file (and in combination with the common general knowledge) in an obvious manner. Thus, inventive step is acknowledged for the subject-matter of claims 1 to 6.

Claims 7 to 9 (not entitled to the earliest priority date)

30. For subject-matter not entitled to the claimed earliest priority date (cf. point 7 *supra*), the closest prior art document is represented by document D3, which discloses the production of a recombinant pC polypeptide and the presence of serological forms of this pC polypeptide (cf. point 9 *supra*). Starting from this closest prior art, the technical problem to be solved is considered to be the provision of an alternative vaccine. The solution to that problem is a vaccine containing an immunogen which is a mixture of different serological forms of non-denaturated

B. burgdorferi pC polypeptide, which said pC polypeptide is a recombinant polypeptide produced in transformed host cells as proposed in claims 7 to 9 (the latter insofar as dependent on claims 7 to 8, cf. Section X *supra*). For the same reasons than the ones given in points 20 and 21 above, in the board's judgment the technical problem is satisfactorily solved.

31. However, document D3 neither suggests combining the serological forms in a vaccine nor the relevance of maintaining the serological forms in a non-denaturated conformation (cf. points 9 to 13 *supra*). Nor can any such suggestion be derived in an obvious manner from the prior art on file (cf. points 23 to 28 *supra*). Therefore, in the board's judgment the subject-matter of claims 7 to 9 as a whole involves an inventive step.

Article 83 EPC; sufficiency of the disclosure

32. As stated for the priority document P1 in points 3 to 6 above, at the earliest priority date the skilled person was in a position to achieve without undue burden the claimed subject-matter, i.e. a vaccine comprising a mixture of different serological forms of non-denaturated *B. burgdorferi* pC polypeptide. There is no evidence on file to support the respondent's allegations that this vaccine is not effective (cf. points 20 and 21 *supra*). Thus, the board considers that the requirements of Article 83 EPC are fulfilled.

Conclusion

33. The patent discloses the invention in a manner sufficiently clear and complete for it to be carried

out by the person skilled in the art (Article 83 EPC) and the claimed subject-matter as a whole is novel (Article 54 EPC) and involves an inventive step (Article 56 EPC). Thus, the board considers that the main request for all the designated Contracting States except ES complies with the requirements of the EPC.

Claims for the Contracting State ES

34. The same conclusions apply to the claims for ES.

Adaptation of the description

35. The amendment of the description pages 3 to 5, 7 and 8 was requested by the appellant. The respondent agreed to the requested amendments but requested, however, that the examples of the description be referred to as "reference examples" (cf. Section XIII *supra*).

36. The examples of the patent in suit disclose a non-denaturing purification method for the pC polypeptide which might be used to isolate and purify this polypeptide from different *B. burgdorferi* strains so as to obtain the claimed non-denatured serological mixture. They also disclose the protective effect of the pC polypeptide which, in the absence of evidence to the contrary, might be assumed to be achieved with the claimed mixture as well. A method for production and expression of recombinant pC polypeptide is also exemplified. Although none of the examples disclose the specific claimed subject-matter, they exemplify the means for achieving it and they provide technical support for the claimed (protective) effect. Thus, these examples are considered not to be "reference

examples", since they actually belong to the solution of the technical problem underlying the patent in suit. Therefore, the respondent's request is refused.

37. The amendments as requested by the appellant result in an appropriate adaptation of the description to the main request and they are in compliance with the requirements of Article 123(2) EPC.

Order

For these reasons it is decided that:

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 main request for all designated states except ES filed with the statement of grounds of appeal, the claims of the main request for the designated state ES and pages 3 to 5, 7 and 8 of the description, both as filed at the oral proceedings, page 2, 6 and 9 to 13 of the description as granted, and the two figures as granted.

The Registrar:

The Chairman:

A. Wolinski

T. Mennessier