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D E C I S I O N
of 8 March 2005

Case Number: T 1146/02 - 3.3.04

Application Number: 96910019.7

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Language of the proceedings: EN

Title of invention:

Vaccines containing a saponin and a sterol

Patentee:

SMITHKLINE BEECHAM BIOLOGICALS S.A.

Opponent:

Chiron Corporation

Headword:

Vaccines containing a saponin and a sterol/SMITHKLINE BEECHAM

Relevant legal provisions:

EPC Art. 123(2)(3), 83, 54, 56

EPC R. 35(12)

Keyword:

"Main request: added subject-matter (no)"

"Broadening of the scope of protection (no)"

"Sufficiency of disclosure (yes)"

"Novelty (yes)"

"Inventive step (yes)"

Decisions cited:

T 0014/83, T 0939/92

Catchword:

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Case Number: T 1146/02 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 8 March 2005

Appellant: SMITHKLINE BEECHAM BIOLOGICALS S.A.
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
18 September 2002 concerning maintenance of
European patent No. 0822831 in amended form.

Composition of the Board:

Chair: U. M. Kinkeldey
Members: R. E. Gramaglia
G. E. Weiss

Summary of Facts and Submissions

I. European Patent No. 0 822 831 (application No. 96 910 019.7) relating to vaccines containing a saponin and a sterol was granted on the basis of 14 claims, of which claim 1 read as follows:

"1. A vaccine composition comprising an antigen, an immunologically active saponin fraction derived from the bark of *Quillaja Saponaria Molina*, and a sterol, characterised in that the ratio of saponin:sterol is from 1:1 to 1:100 (w/w)."

II. Notice of opposition was filed by the opponent requesting the revocation of the European patent on the grounds of Article 100(a), (b) and (c) EPC.

III. Claim 1 of the appellant's main request in opposition proceedings read as follows:

"1. A vaccine composition comprising an antigen, QS21, and a sterol, characterised in that the ratio of QS21:sterol is from 1:1 to 1:100 (w/w) and in that the QS21 is at least 90% pure."

Claims 2 to 8 related to specific embodiments of the vaccine composition of claim 1. Claims 9 to 11 were addressed to medical uses of the composition of claims 1 to 8. Claim 12 was to a process for making the vaccine composition of claims 3 to 8.

The opposition division came to the conclusion that the claims of the main request and of the first and second auxiliary requests, while complying with the

requirements of Articles 123(2)(3) EPC, 84 EPC, 54 EPC and 56 EPC, did not satisfy the requirements of Article 83 EPC. This was because claim 1 of these requests covered not only the exemplified liposomes including a sterol and QS21, but also oil-in-water emulsions including a sterol and QS21. In the opposition division's view, however, the patent in suit failed to disclose any process for arriving at said oil-in-water emulsions including a sterol and QS21 and the skilled person wishing to prepare said emulsions had to exert inventive activity. However the grounds for opposition did not prejudice the maintenance of the patent as amended according to the third auxiliary request, the claims of which were limited to vaccine compositions in the form of liposomes.

IV. As announced in a previous letter, the respondent was not represented at the oral proceedings held on 8 March 2005 before the board, during which the appellant filed a new main request consisting of claims 1 to 12 identical (were it not for the correction of two clerical errors in claim 9) to claims 1 to 12 of the main request before the opposition division and replacement pages 2 and 13 of the patent specification.

V. The following documents are referred to in this decision:

(D1) Lipford G.B. et al., Vaccine, Vol. 12, No. 1, pages 73-80 (1994);

(D3) W0-A-96/11711;

(D6) US-A-5,057,540;

- (D8) EP-A-0 231 039;
- (D10) Second declaration of V. Henderickx dated 30 May 2002;
- (D12) Kensil C.R. et al. in "Vaccine Design: The Subunit and Adjuvant Approach", Editors Powell & Newman, Plenum Press, pages 525-541 (1995);
- (D13) W0-A-99/12565;
- (D14) W0-A-90/14837;
- (D15) W0-A-92/00081;
- (D16) Schmidt P.C. et al., Acta Pharm. Technol., Vol. 35, No. 1, pages 34-37 (1989);
- (D17) US-A-3,085,939;
- (D18) Lövgren K. et al., Biotechnology and Applied Biochemistry, Vol. 10, pages 161-172 (1988);
- (D19) Bomford R., Int. Archs. Allergy appl. Immun., Vol. 63, pages 170-177 (1980).

VI. The submissions by the appellant, insofar as they are relevant to the present decision can be summarized as follows:

Article 123(3) EPC

- The introduction of the QS21 purity in claim 1 of the main request represented a narrowing of the protection conferred by the claim as granted.

Clarity - "at least 90% pure"

- At the priority date of the patent in suit it was not possible to produce QS21 synthetically. Hence, it had to be extracted from natural sources. Accordingly, the feature "at least 90% pure" had to be interpreted in relation to the field of natural products as meaning that QS21 must be "at least 90% pure" when isolated from its natural source.
- The requirement for the QS21 to be "at least 90% pure" could only refer to the starting purity of the QS21 used in the manufacture of the claimed composition, rather than to the purity of the QS21 within the composition itself. In fact, the specification of the patent made it clear that the purity limitation related to the other contaminants accompanying QS21.
- The impurities associated with QS21 were known to the skilled person to be distinct from those associated with the sterol and the antigen. Therefore, the skilled person could easily obtain HPLC elution profiles as depicted in Figure 4B of document (D6) and Figure 2 of document (D12) from formulated vaccine compositions falling within the definition of the subject-matter of claim 1 and check for their presence. Hence the skilled person

was in a position to experimentally verify whether a composition fell within the scope of protection provided by claim 1 or not.

Sufficiency of disclosure

- The respondent had provided no evidence to substantiate a serious doubt that oil-in-water emulsions falling within claim 1 were impossible or unduly burdensome to make or would not exhibit the required properties.
- Examples of protocols for producing oil-in-water emulsions were available from the prior art as witnessed by documents (D14) to (D17).
- Test report (D10) demonstrated that oil-in-water emulsions comprising QS21 and cholesterol had the desired properties.
- Document (D13) was the only evidence relied upon by the opposition division for its finding that at the relevant date of the patent in suit the skilled person could not make the claimed oil-in-water emulsions without inventive skill. However, document (D13), a later filed patent application filed by the appellant, constituted an (inventive) selection falling within the scope of claim 1, but this did not mean that oil-in-water emulsions as claimed were not reproducible at the relevant date of the claimed invention. If anything, document (D13) showed that the oil-in-water emulsions as claimed worked (see Examples 2, 5, 8 and 9).

Novelty (Article 54 EPC)

- None of the documents (D8), (D18), (D19) and (D3) disclosed compositions containing QS21 in the required purity. Accordingly, these documents could not prejudice the novelty of the claims of the main request.

Inventive step

- Document (D6) represented the closest prior art since it related to isolated QS21 fraction and its use as an adjuvant. However, QS21 isolated according to document (D6) had two drawbacks, namely (i) it was unstable and (ii) it showed toxicity (e.g., necrosis at the injection site) when used as adjuvant. The problem to be solved was therefore the provision of an improved formulation of QS21 which suffered less the disadvantages of instability and toxicity while retaining the adjuvant properties of the molecule. Whereas document (D6) dealt with overcoming the toxicity problems arising from using crude Quil A (see column 3, lines 40-46), i.e. that QS21 was the solution to the toxicity problems arising with crude Quil A, the patent in suit was the first to recognise the above problems (i) and (ii) with QS21 and to propose a solution to them.
- It was true that the patent in suit and document (D10) also related to formulations which lacked the antigen, contrary to the requirements of claim 1. However, the purpose of these data was to show that the toxic effect of QS21 was reduced by the presence of a sterol. This was independent from the adjuvant

(immunostimulant) effect which, incidentally, was also shown by the appellant's data to be kept in the presence of a sterol (see patent, Examples 1.8, 1.9 and 2). It was surely not necessary to test formulations containing an antigen in every instance to make a compelling showing of the detoxifying effect of a sterol on QS21.

VII. The submissions made by the respondent, insofar as they are relevant to the present decision can be summarized as follows:

Article 123(3) EPC

- The introduction of the QS21 purity in claim 1 of the main request raised an issue under Article 123(3) EPC, since it broadened the protection conferred by the claim as granted.

Clarity - "at least 90% pure"

- The requirement in claim 1 for the QS21 to be "at least 90% pure" rendered it unclear in the absence of an indication whether "at least 90% pure" related to the starting purity of the QS21 used in the manufacture of the claimed composition or to the purity of the QS21 within the composition itself. Therefore, it was not possible for the skilled person to determine whether or not a given composition fell within the scope of claim 1, as he/she would not be able to distinguish between impurities that were present in the starting QS21 composition and the impurities associated with the other components of the composition.

- Even if "at least 90% pure" related to the starting QS21 used in the manufacture of the composition, the claims were still unclear as there was no explanation as to how the percentage purity of QS21 had to be calculated.
- The wording "at least 90% pure" in the claim also rendered the ratio saponin:sterol used in the claim unclear.

Sufficiency of disclosure

- The patent only disclosed active compositions in which QS21 and cholesterol were under the form of liposomes.
- The attempt to produce a vaccine composition without the formation of liposomes, by combining QS21 with a soluble derivative of cholesterol, had been acknowledged in paragraph [0028] of the patent to have failed.
- Document (D13), an appellant's later patent application, stated on page 4 that the similar efficacy of the QS21/cholesterol oil-in-water emulsions as compared to the liposomal compositions was *surprising*, thereby implying that inventive skill was required to formulate a vaccine composition which did not use a liposome. Furthermore, the document solely related to oil-in-water emulsions which (a) included the adjuvant 3D-MPL and (b) had the QS21 in the aqueous phase and cholesterol in the oil phase. There was no

evidence that other types of oil-in-water emulsions were useful.

Novelty

- Documents (D8), (D18), (D19) and (D3) all disclosed compositions comprising QS21 and a sterol in a ratio of between 1:1 and 1:100 as required by claim 1. The only feature that could confer novelty was "at least 90% pure". However, since the said feature was unclear it could not therefore distinguish the compositions of documents (D8), (D18), (D19) and (D3) from the compositions covered by claim 1 and it was impossible for the skilled person to establish whether or not a composition contained QS21 in this purity. Accordingly, the claims lacked novelty.

Inventive step

- The technical effects argued by the appellant, namely detoxification and stabilisation of QS21 without loss of its adjuvant effect was shown neither in the patent nor in document (D10) since these documents dealt with formulations devoid of the antigen, contrary to the requirement of claim 1 at issue.
- The effects were merely shown for the vaccines in the form of liposomes.
- Mixing QS21 with a sterol, without the formation of a saponin/sterol structure did not achieve the promised technical effects, as shown by paragraph [0028] of the patent.

VIII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the new main request submitted at the oral proceedings.

The respondent requested in writing that the appeal be dismissed.

Reasons for the Decision

Article 123(2)(3) EPC

1. Claim 1 of the main request is a combination of claims 1, 2 and 4 as originally filed, respectively of claims 1 and 4, with the feature "and in that the QS21 is at least 90% pure". The latter feature finds basis on page 1, lines 28 to 29, of the application as filed (published WO application). Claims 3, 7, 8 and 10 to 12 are identically contained in the claims as originally filed. The same claims and claims 4 to 6 and 9 are identically contained in the claims as granted. Claim 2 is based on page 2, lines 7 to 9 of the application as filed. Claim 4 finds a basis on page 2, lines 19 to 20 of the application as filed. Claim 6 finds basis at page 2, lines 34 to 38 of the filed application. Claim 9 finds basis on page 1, lines 1 to 2 and page 5, lines 16 to 17 of the application as filed.

2. The respondent argues that introduction of the QS21 purity in claim 1 of the main request raises an issue under Article 123(3) EPC, since at 90% purity, the saponin:sterol ratio becomes 0,9:1 and the ratio 1:100

becomes 0,9:100, thereby broadening the protection conferred by the claim as granted.

3. The board cannot concur with this respondent's view. Claim 1 of the patent as granted refers to "an immunologically active saponin fraction derived from the bark of Quillaja Saponaria Molina" and is devoid of any explicit statement as to the ratio saponin:sterol. In the board's judgement therefore the protection conferred by claim 1 of the main request, exemplifying the saponin, i.e. QS21 and its purity entails to narrowing the protection conferred as compared to the granted claim.
4. The board is thus satisfied that claim 1 of the main request complies with the requirements of Article 123(2) and (3) EPC.

Clarity - "at least 90% pure"

5. Claim 1 of the main request is directed to vaccine compositions comprising an antigen, QS21 and a sterol wherein the ratio of QS21:sterol is from 1:1 to 1:100 (w/w) and the QS21 is **at least 90% pure**. It is the respondent's view that this feature is unclear.
6. In a first line of argument the respondent maintains that the requirement in claim 1 for the QS21 to be "at least 90% pure" renders it unclear in the absence of any indication whether "at least 90% pure" related to the starting purity of the QS21 used in the manufacture of the claimed composition or to the purity of the QS21 within the composition itself. Hence, he/she would not be able to distinguish between impurities that were

- present in the GS21 that was used to formulate the composition and the impurities in other components of the composition. Therefore, it is not possible for the skilled person to determine whether or not a given composition falls within the scope of claim 1.
7. In the context of Article 84 EPC, the meaning of a term or expression used in a feature of a claim depends in particular on the definition thereof generally accepted by those skilled in the relevant art, as established by Rule 35(12) EPC, last sentence, requiring in general terms that use should be made of the technical terms generally accepted in the field in question.
 8. The patent in suit (see paragraph [0002]) defines QS21 as a fraction obtained by subjecting to HPLC an aqueous extract of the bark of the Quillaja Saponaria Molina tree according to document (D6), disclosing the isolation of QS21 from natural sources. QS21 (termed "QA-21" in document (D6)) is by definition the 21st fraction eluting from the HPLC column as a very minor component (see *ibidem*, Table 1). The skilled person relevant for elucidating the meaning of the feature "at least 90% pure" when relating to QS21 is thus a person working in the field of the purification of natural products.
 9. Document (D6) in column 4, lines 36 to 42, defines the term "substantially" pure in the context of the saponin fractions, including the QS21 fraction, as meaning "substantially free from compounds naturally associated with the saponin in its natural state and exhibiting constant and reproducible chromatographic response, elution profiles, and biological activity". On lines

- 43 to 54 of the same column, document (D6) sets the experimental standards for substantially pure saponin fractions, including "QA-21", i.e., they should appear as only one major peak or band in defined experimental protocols. Further, it can be derived from the wording of claim 5 of the same document that QA-21 (QS21) is "substantially" pure if one predominant peak comprises 90% or more of the total area of the peaks around the retention time of 51.6 min corresponding to the 21st fraction eluting from the HPLC column.
10. The above definition of the purity of QS21 as a ratio between the area of the predominant peak and the total area of the peaks around it is in line with that adopted in Figure 2 of document (D12), showing different stages of purity of HPLC-purified QS21. It can be seen from this Figure that the secondary peaks relating to compounds naturally associated with the QS21, i.e., contaminant saponins, vanish as purity reaches 98% (see Figure 2D).
 11. The board therefore concludes that the feature "at least 90% pure" in claim 1 and on page 2, line 20 of the patent in suit is clear to the skilled person and means that the starting product, i.e., QS21 should contain 10% or less naturally associated substances, i.e., the other saponin contaminants as detectable during the purification process as secondary peaks around the QS21 main peak.
 12. Moreover, the respondent's argument that it is not possible for the skilled person to determine whether or not a given composition falls within the scope of claim 1 is not convincing. This is because the HPLC

- elution profiles as depicted in Figure 4B of document (D6) and Figure 2 of document (D12) can easily be obtained by the skilled person from formulated vaccine compositions falling within the definition of the subject-matter of claim 1. The saponin contaminants associated with QS21, known to be distinct from those found from sterol and antigen can easily be detected and quantified from this HPLC elution profile. In conclusion, the skilled person is in a position to experimentally verify whether or not a given composition falls within the scope of protection provided by claim 1.
13. In the respondent's view, the claims are also not clear in the absence of any explanation therein as to how the percentage purity of QS21 should be calculated. However, the skilled person would calculate this percentage as a ratio between the area of the predominant peak and the total area of the peaks around the retention time of 51.6 min corresponding to the 21st fraction eluting from the HPLC column (see points 9 to 11 supra).
14. Finally, since the wording "at least 90% pure" is clear, the respondent's line of argument that the introduction of the concept of purity in the claim renders the ratio saponin:sterol used in the claim unclear, must fail.
15. In view of the foregoing, the board concludes that no case of lack of clarity has been made out.

Sufficiency of disclosure

16. The opposition division decided that the claims of the main request as presently before the board did not

- satisfy the requirements of Article 83 EPC because claim 1 covered the oil-in-water emulsions referred to on page 2, line 49 of the patent in suit, but the disclosure of the patent was insufficient to allow a skilled person to make these oil-in-water emulsion-based adjuvant formulations.
17. However, in paragraph 5.8 of his letter dated 6 June 2003 the respondent submitted that "The opponent does not doubt that the techniques required for manufacturing oil-in-water emulsions were well known at the priority date. Nor does the opponent doubt that a skilled person could have formulated QS21 and cholesterol onto an oil-in-water emulsion had they been asked to do so". Therefore, the respondent's attack under Article 83 EPC is not directed against the manufacture of oil-in-water emulsions comprising QS21 and cholesterol **in general**. The board agrees as well that the skilled person, even in the absence of detailed instructions or examples in the patent, could have formulated QS21 and cholesterol as an oil-in-water emulsion in the light of e.g. documents (D14) to (D17), disclosing the preparation of oil-in-water emulsions in general.
18. The respondent rather argues that only oil-in-water emulsions which (a) include the adjuvant 3D-MPL and (b) have a particular partitioning of QS21 and cholesterol (QS21 in the aqueous phase and cholesterol in the oil phase) would exhibit the desired useful properties.
19. To support his case the respondent relied on document (D13), a later patent application filed by the patentee stating on page 4 that the observed similar efficacy of

the QS21/cholesterol oil-in-water emulsions as compared to the liposomal compositions was "surprising". This implied, in the respondent's view that further inventive skill was required to formulate an adjuvant composition not in the form of liposomes, but in the form of an oil-in-water emulsion which (a) included the adjuvant 3D-MPL and (b) had the QS21 in the aqueous phase and cholesterol in the oil phase, namely the only non-liposome QS21/cholesterol adjuvant formulation having the desired useful properties.

20. The board firstly observes in passing that making a selective invention over an earlier broader patent does not necessarily mean that the earlier patent is insufficient. Secondly it is noted that 3D-MPL referred to in document (D13) is merely an optional further adjuvant/immunomodulator (see paragraph bridging pages 5 and 6 and claim 9 of document (D13)), which is not critical for achieving the useful stability and non-toxicity properties of the claimed QS21/sterol adjuvant. This is shown by Example 5 of document (D13) (see page 22, Table 7 and page 23, lines 10-15), according to which the oil-in-water adjuvant SB62'c (comprising cholesterol) turns out to be better than SB62' (devoid of cholesterol) in terms of useful properties, despite 3D-MPL is present in both SB62'c and SB62' (see Table 7: "MPL" in combination with page 13, line 19: "3D-MPL"). Therefore, the respondent's contention that 3D-MPL is a critical component for obtaining useful non-liposome QS21/cholesterol adjuvants is not convincing.

21. The respondent also maintains that a particular partitioning of QS21 and cholesterol (QS21 in the

- aqueous phase and cholesterol in the oil phase) was required in order that QS21/cholesterol adjuvants exhibit the desired useful properties. To buttress the above view, the respondent referred to paragraph [0028] of the patent in suit disclosing an attempt to produce a useful adjuvant composition by combining QS21 with a soluble derivative of cholesterol, which attempt was acknowledged to have failed.
22. In the experiment described in paragraph [0028] of the patent, the sterol has been modified so as to behave as a bilayer-forming phospholipid able to form a stable suspension of liposomes, bearing the sterol moiety. However, something went wrong and the composition did not exhibit the desired useful properties.
23. In the board's judgement, completely altering the chemical nature of a **critical** molecule, in this case the sterol referred to in claim 1 at issue, which is normally lipophilic (see page 5, line 3: "cholesterol is insoluble in aqueous solution") to make it water-soluble (up to 60 mg/ml) by attachment thereto of a long hydrophilic chain, is not the way the **cautious** skilled person would normally proceed. The (not completely unexpected) failure reported in paragraph [0028] of the patent cannot thus be considered as a proof that other forms of QS21/sterol adjuvants do not deliver the promised advantages. Paragraph [0010] of the patent in suit as well as documents (D10) (see "composition 8") and (D13), containing data showing the advantageous properties of compositions in the form of oil-in-water emulsions, rather suggests that the carrier (liposomes, microspheres (i.e., oil-in-water emulsions), etc) is not critical.

24. In conclusion, the claims satisfy the requirements of Article 83 EPC.

Novelty

25. The board has concluded in point 11 supra that the feature "at least 90% pure" has to be read in the context of contamination with other saponins contained in the natural extracts. Lack of novelty can therefore only occur if a prior art document discloses compositions comprising, inter alia, QS21 in the purity required by claim 1, the latter being a distinguishing (and measurable) feature (see point 12 supra).
26. Documents (D8) and (D18) disclose immuno stimulating complexes (Iscom's) which are stable particulate complexes of protein antigens incorporated into cage-like structures obtained by mixing a detergent, a lipid and a saponin. The compositions described in these documents are based on Quil-A (see document (D8), page 3, line 60 and document (D18), page 163, lines 10 to 16), cholesterol and an antigen. It is the respondent's view that these compositions fall under claim 1 because they exhibit a ratio QS21:sterol of 1:60 to 1:20.
27. However, according to document (D6), column 10, Table 1, QS21 ("QA-21") is a fraction (3.7%) of Quil-A ("Superfos"). Accordingly, compositions comprising "Quil-A" do **not** meet the requirement that the QS21 be at least 90% pure.

28. Accordingly, in the board's judgement documents (D8) and (D18) do not prejudice the novelty of claim 1 of the main request.
29. As for document (D3), a document relevant under Article 54(3) EPC, it discloses Iscom preparations based on certain fractions of Quil-A, including fraction QH-C, of which the purification is described in Example 1 thereof. The respondent argues that Figure 1 of document (D3) shows that the QH-C fraction is located in the most hydrophobic Quil-A fraction and therefore must contain QS21 in view of the fact that Figure 1 of document (D6) also shows that QS21 is located in the most hydrophobic fraction of Quil-A.
30. However, a comparison of the experimental conditions applied for deriving the data shown in the two figures reveals major differences, such as for example the use of HPLC (documents (D3)) vs. reverse phase HPLC (document (D6)). Furthermore, it is apparent from Figure 1 of document (D3) that the QH-C fraction constitutes a quite narrow selection of the hydrophobic end of the retention profile. Therefore, in the board's judgement, a comparison of the elution profiles of Figures 1 of documents (D3) and (D6) does not make sense and any inferences from their comparison cannot be technically relevant.
31. In conclusion, there is no evidence before the board that the QH-C fraction referred to document (D3) comprises QS21, let alone "at least 90% pure" QS21.
32. It is established case law of the Boards of Appeal that where lack of novelty is alleged, the burden of proof

- lies with the party claiming that the information in question was made available to the public before the relevant date.
33. Since the respondent has also not discharged its burden of proof to establish that fraction QH-C contains QS21 in the required purity, the board concludes that document (D3) is not prejudicial for the novelty of claim 1.
34. A similar situation as for document (D3) arises in relation to document (D19), which discloses liposomes based on Quillaja saponins obtained from three different sources (see document (D19), page 171, under the heading "Material Tested for Adjuvanticity") and which are confirmed to be chemically inhomogeneous and to contain a mixture of triterpene glycosides (see page 175, sentence bridging l-h and r-h columns).
35. It cannot be derived from document (D19) that QS21 is at all present in the disclosed liposomes, let alone in the concentration as required in claim 1 of the main request. Accordingly, the board considers that with respect to the novelty of claim 1 of the main request over document (D19), the respondent has not discharged its burden of proof to establish that fraction QH-C contains QS21. The board therefore concludes that document (D19) is not prejudicial for the novelty of claim 1.
36. In conclusion, the claims of the main request satisfy the requirements of Article 54 EPC.

Inventive step

37. The patent in suit is concerned with the use of the saponin QS21 as an adjuvant in vaccine compositions and claim 1 of the main request is directed to a vaccine composition comprising an antigen, the saponin QS21 and a sterol. It is stated in the patent that purified QS21 has two drawbacks, namely (i) it is unstable (see page 2, line 24) and (ii) it exhibits toxicity (e.g., necrosis at the injection site) when used as adjuvant (*ibidem*, lines 10-12). The patent in suit thus purports to overcome said drawbacks.
38. The parties propose two possible starting points for the problem-solution approach, i.e. in a first one, document (D6) or (D12) represents the closest prior art, whereas in a second one either of documents (D1), (D8) or (D18), disclosing immunogenic compositions containing an antigen, the saponin Quil A and a sterol, represents the closest prior art. It therefore needs to be established which of the above documents represents the closest prior art for assessing the inventive step.
39. Document (D8) and (D18) deal with the preparation of immunogenically enhanced formulations of Quil A-based vaccines in the form of Iscom's. Document (D1) deals with a similar specific enhanced formulation of Quil A-based vaccines, namely in the form of liposomes. However, documents (D1), (D8) and (D18) are silent as to the objective to reduce drawbacks (i) and/or (ii) emphasised in point 37 *supra*.
40. Document (D6) addresses the same drawbacks (i) and (ii) dealt with in the patent in suit. The document indeed

discloses the purification of at least 22 fractions with saponin activity from the crude aqueous extract termed Superfos ("Quil A") from a Quillaja saponin preparation. Four saponins were identified as predominant in Quil A, i.e. those contained in fractions QA-7, QA-17, QA-18 and QA-21 (the latter being identical to fraction QS21 used in the patent in suit). Animals injected with QA-21 appeared mildly ill initially but appeared to recover fully within a few hours after injection, unlike those injected with Quil-A (see the passage bridging columns 21 and 22). The loss of adjuvant activity upon hydrolysis is referred to in column 22, lines 36-49 of this document.

41. The problem of (i) the instability of QS21 to base-mediated hydrolysis and (ii) toxicity have also been addressed in the review document (D12), co-authored by one designed inventor of document (D6) (see section 3.3. bridging pages 529 and 530 and page 538, first paragraph, respectively).
42. Both documents (D6) or (D12) thus represent prior art closer to the claimed subject-matter than documents (D1), (D8) and (D18). The board considers document (D6) as the appropriate starting point for the problem-solution approach, noting however, that any reasoning would not change by departing from document (D12).
43. The structural difference between the subject-matter of claim 1 and the compositions disclosed in document (D6) is the addition of a sterol in a specific ratio to the immunogenic composition containing QS21 of document (D6). In view of the achieved technical effect the problem to be solved can therefore be formulated as the

provision of QS21 containing immunogenic compositions exhibiting decreased reactogenicity (toxicity/necrosis) at the injection site and enhanced stability of QS21 to base-mediated hydrolysis, while the adjuvant effect is maintained (see patent page 2 lines 22 to 26).

44. In view of the experimental results presented in Examples 1.4 to 1.6 and 1.8, 1.9 and 2 of the patent in suit and those filed during the opposition proceedings in the form of document (D10) (compare the figures for Group 2 (QS21 alone) with the figures for Groups 6, 7 and 8 (QS21 with cholesterol in various compositions), wherein the reduction in necrosis in the compositions containing cholesterol is evident), the board is satisfied that the above problems have been solved.
45. The respondent argues that the technical effects invoked by the appellant, namely detoxification and stabilisation of QS21 without loss of its adjuvant effect are shown neither in the patent nor in document (D10) since these documents dealt with formulations devoid of an antigen, contrary to the requirement of claim 1 at issue.
46. However, the purpose of these data relating to formulations lacking the antigen is to show that the toxic effect of QS21 is reduced and its stability is enhanced by the presence of a sterol. These effects, relevant to the inventive step issue, occur **independently** from the adjuvant (immunostimulant) effect of the composition, which adjuvant effect is also shown by the patent (see Examples 1.8, 1.9 and 2), albeit less relevant to the inventive step issue. Therefore, in the board's view, the data given in the

- patent in suit and in document (D10) are suited to demonstrate the detoxifying and stabilizing effect of a sterol on QS21, which technical effects are in turn suited to support inventive step.
47. The respondent also maintains that the advantageous effects are merely shown for the vaccines in the form of liposomes. However both documents (D10) (see "composition 8") and (D13) contain data showing the advantageous properties of compositions in the form of oil-in-water emulsions. It is true that these compositions contain 3D-MPL, however the fact that 3D-MPL is not involved in reducing the toxic effect of QS21 or in enhancing its stability has already been dealt with under point 20 supra in the context of sufficiency of disclosure.
48. Finally the respondent relies on paragraph [0028] of the patent for arguing that claim 1 covers embodiments which do not achieve the promised technical effects, and which are thus not inventive according to decision T 939/92 (Agrevo; OJ EPO 1996, 309).
49. However, the board does not see the factual situation of the present case in the framework of the above decision, but rather in that of the case law (see decision T 14/83, OJ EPO 1984, 105) that it is of no consequence that one specific set of parameters within a claim **occasionally** leads to a formulation not having the advantages promised by the patent (see paragraph [0028] of the patent), so long as **substantially** all embodiments covered by a claim provide a solution to the problem to be solved. An occasional failure can thus be "forgiven" since there is ample evidence before

- the board, not contradicted by any data from the respondent, that substantially all of the claimed formulations do provide a solution to the problems addressed by the patent.
50. Moreover, as emphasized under point 23 supra in the context of sufficiency of disclosure, completely altering the chemical nature of a molecule **critical** to obtaining an advantageous technical effect, in this case the sterol referred to in claim 1 at issue, which is normally lipophilic to make it water-soluble by attachment thereto of a long hydrophilic chain, is neither the way the **cautious** skilled person would normally proceed, nor the best manner for increasing his/her hope to succeed. Therefore, the (not completely unexpected) failure reported in paragraph [0028] of the patent cannot be considered as a proof against the fact that substantially all the claimed QS21/sterol adjuvants deliver the described advantages.
51. The only issue left to be decided is thus to whether or not the prior art rendered obvious to the skilled person to add to the immunogenic QS21 compositions of document (6) a sterol in the ratio indicated, i.e. QS21:sterol from 1:1 to 1:100 (w/w), in order to solve problems (i) and (ii) stated in point 37 supra.
52. Document (D6) does not propose any solution to problems (i) and (ii), let alone the sterol-based one. Only document (D12) (see page 529, last line to page 530, first line) proposes a solution for overcoming drawback (i) (hydrolysis) by using a lower pH and a higher QS21 concentration in the formulation, however, this points

to another direction than the solution stated in claim 1.

53. Furthermore, as stated in point 26 above, certain cited documents disclose saponin, i.e. Quil A, containing immunogenic compositions which contain a sterol, inter alia documents (D1), (D8) and (D18). Documents (D8) and (D18) disclose, however, the sterol to be essential for the formation of Iscom's (see document (D8), page 2 line 37 and document (D18), abstract). Accordingly, these documents disclose the use of sterol in Quil A containing immunogenic preparations for a different purpose. Similarly, document (D1) discloses the use of cholesterol in Quil A-containing immunogenic compositions in the form of liposomes. The document is however silent as to the purpose of the addition of cholesterol.

54. In summary the board concludes that the use of sterols in QS21-containing immunogenic preparations as claimed for achieving increased hydrolysis stability and decreased toxicity of QS21, while retaining the adjuvant activity thereof has not been rendered obvious to the skilled person by any prior art document or combination thereof. The claims of the main request also satisfy the requirements of Article 56 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 as amended in the following version:
 - description: pages 2 and 13 filed at the oral proceedings, pages 3 to 12 of the patent specification;
 - claims 1 to 12 filed as "new main request" at the oral proceedings.

The Registrar:

Chair:

P. Cremona

U. M. Kinkeldey