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Datasheet for the decision of 12 January 2022

Case Number: T 2175/17 - 3.3.08

Application Number: 08864247.5

Publication Number: 2235159

IPC: C12N1/20, A61K39/04, C12P19/04, C08B37/00, A61K39/00, C12Q3/00

Language of the proceedings: EN

Title of invention:
PURIFICATION PROCESSES FOR OBTAINING CPS FROM STREPTOCOCCI

Patent Proprietor:
GlaxoSmithKline Biologicals SA

Opponent:
Pfizer Inc.

Headword:
Method of purifying CPS from S. agalactiae/GLAXOSMITHKLINE

Relevant legal provisions:
RPBA Art. 12(4)
EPC Art. 123(2), 84, 87, 56

Keyword:
Main Request - requirements of the EPC met (yes)

Decisions cited:
G 0009/91, G 0010/91, G 0002/98

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 2175/17 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 12 January 2022

Appellant: (Patent Proprietor)	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart (BE)
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Representative:	Ricol, David Markus, Marc Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 11 July 2017 revoking European patent No. 2235159 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	D. Pilat
	A. Bacchin

Summary of Facts and Submissions

I. European patent No. 2 235 159 is based on European patent application No.08864247.5 (published as WO 2009/081276 on the 2 July 2009). The patent was opposed on the grounds of Article 100(a) in conjunction with Articles 54 and 56 EPC, and of Articles 100(b) and (c) EPC. An opposition division decided that the main request before it was unclear under Article 84 EPC, that Auxiliary request 1 offended Article 123(2) EPC, that auxiliary request 2 lacked an inventive step, that auxiliary requests 3 to 8 lacked clarity and that auxiliary requests 9 and 10 offended Article 123(2) EPC. Auxiliary request 11 submitted during the oral proceedings in opposition was not admitted. The patent was revoked.

II. The patent proprietor (appellant) lodged an appeal. With its statement of grounds of appeal, it submitted a main request and auxiliary requests 1 to 5.

III. Opponent (respondent) replied to the statement of grounds of appeal.

IV. In reply to the respondent's response, appellant filed further submissions.

V. The parties were summoned to oral proceedings. In a communication issued in preparation of the oral proceedings, the parties were informed of the board's provisional, non-binding opinion on some of the legal and substantive matters of the case.

VI. With a letter dated 20 December 2021, appellant replied to the board's communication and submitted auxiliary

request 6 corresponding to the claims of the main request and an amended description page 9.

VII. Oral proceedings took place on 12 January 2022.

VIII. Claim 1 according to the main request reads as follows:

1. A method for purifying a capsular polysaccharide from *Streptococcus agalactiae* comprising the following steps:

(i) Alcoholic precipitation of contaminating proteins and/or nucleic acids in the presence of a divalent cation;
(ii) diafiltration;
(iii) filtration using a protein adherent filter which is an activated carbon filter immobilised in a matrix to which protein and DNA adheres but to which the capsular polysaccharide does not adhere;
(iv) re-N-acetylation;
(v) diafiltration;

wherein step (iii) is preceded by steps (i) and (ii) and followed by steps (iv) and (v), the method does not include a step of cationic detergent treatment to precipitate the capsular polysaccharide followed by a step of re-solubilization of the capsular polysaccharide."

Dependent claims 2 to 14 define particular embodiments of the method of claim 1.

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

P1: US61/008941 (filing date 20 December 2007);
D8: WO2007/052168 (published on 10 May 2007);
D9: WO2008/118752 (published on 2 October 2008);

D12: GB2102291 B1 (published on 24 July 1985);
D15: US2006/0073163 (published on 6 April 2006)

X. The substantive submissions made by the **appellant**, insofar as relevant to the present decision, may be summarized as follows:

Main request (claims 1-14)
Article 123(2) EPC

The reasons and conclusion on added matter with respect to claims 9 to 13 in point 2.2.2 of the decision under appeal were not contested.

Admission of a new line of argument raised against the description under Article 123(2) EPC

The objection of added matter raised by the respondent was based on amended paragraphs [0073] to [0075] of the patent and derived from paragraphs [00161] to [00163] of the patent application. These paragraphs were not objected under Article 123(2) EPC during opposition proceedings (see Case Law of the Boards of Appeal of the European Patent Office 9th Edition, July 2019, Chapter V.A.3.2.1.c). The notice of opposition on page 5 focused on the replacement of the term "Pneumococcus" by the broader term "*Streptococcus*" at paragraph [00161] and on the fact that the conjugates, specified to be from *S. pneumoniae*, had been deleted from the disclosure at paragraphs [00162] and [00163]. These amendments highlighted that the patent application provided no direct and unambiguous disclosure for the subject matter of claims 17 and 18 as granted. This objection constituted a fresh ground whose admission into the appeal proceedings had to be refused in accordance with decision G 10/91, headnote 3. The

objection amounted to a mere description of facts and provided moreover no explanation as to why and how these amended paragraphs added matter (see respondent's reply to the statements of grounds of appeal page 15). This objection was not properly substantiated.

Article 84 EPC

The reasons and conclusion on clarity in point 2.2.1 of the decision under appeal were not contested.

Article 87 EPC

For assessing whether the priority right was valid within the meaning of Article 87(1) EPC, the subject-matter of the claims had to be directly and unambiguously derivable from the disclosure of the invention in the priority document (see Opinion G 2/98 of 31 May 2001).

Claims 43 to 52 of the first priority document P1 (US61/008941) disclosed a method for the production of a purified capsular polysaccharide. These claims explicitly disclosed every step of claim 1, including in claim 44 the step of re-N-acetylation.

Document P1 furthermore disclosed a step of

- alcoholic precipitation in the presence of a divalent cation (see paragraphs [0106] to [0112]),
- filtration, particularly diafiltration, following alcoholic precipitation (see paragraphs [0112] to [0115]),
- cationic detergent treatment, stated to be optional and that "preferred embodiments will exclude detergent precipitation" (seep paragraph [0116]),

- filtration with a protein adherent filter with a filter "to which protein and/or DNA adheres, but to which capsular polysaccharide does not adhere or only weakly adheres. A preferred example of such a filter is a carbon filter" (see paragraphs [0127] and [0036]) and
- re-N-acetylation (see paragraph [0103]).

In preferred embodiments the method for the production of a purified capsular polysaccharide included one or more of the following steps (see paragraphs [0033] to [0036] of document P1).

The different starting material disclosed and defined in claim 43 and paragraphs [0033], [0101] to [0106] of document P1 implicitly needed to be purified. The starting material was nowhere shown to be inextricably linked to the other steps of the claimed method.

The cationic detergent treatment was set to be an optional step of the method, while the diafiltration step, such as the tangential flow diafiltration, was not disclosed to be inextricably linked to the other steps of the claimed method (see paragraphs [0116] and [0113] to [0115] of document P1).

Finally, Example 6 of document Pl exemplified the purification process for GBS polysaccharides using the steps of the claimed method. In particular, it proposed the use of a depth filtration on a CUNO BioCap 2000 1300 cm^2 capsule to remove residual protein contaminants (see paragraph [0414]).

There was a clear, explicit and sequential disclosure of the precise steps of the claimed process in both the specification and claims of document Pl. They both

disclosed the same invention. Thus, the claims of the main request were entitled to claim priority from document P1.

Article 56 EPC

Document D8 represented the closest prior art. It concerned the purification of capsular polysaccharide from *Streptococcus agalactiae*.

It disclosed a method for purifying capsular polysaccharide which included an alcoholic precipitation and cation exchange, diafiltrations, cationic detergent treatment and a re-solubilization (see page 5, 2nd paragraph and pages 8 to 12). After re-solubilisation, the polysaccharide could be further treated to remove contaminants. This was particularly important in situations where even minor contamination is not acceptable (e.g. for human vaccine production). This typically involved one or more steps of filtration e.g. depth filtration, filtration through activated carbon, size filtration and/or ultrafiltration (see document D8, page 12, lines 13 to 21).

The difference between the method of claim 1 and document D8 was that the claimed method did not include a step of cationic detergent treatment to precipitate the capsular polysaccharide followed by a step of re-solubilization of the capsular polysaccharide.

This difference provided a simplified method for purification of capsular polysaccharide from *S.agalactiae* with a high level of purity. The simplification resulted in a faster and a less cumbersome method for purifying capsular polysaccharide where the number of methods steps was reduced, and/or

one or more of the time consuming steps was exchanged or deleted.

The objective technical problem solved by the claimed method was the provision of a more simple method for purifying capsular polysaccharide from *Streptococcus agalactiae* with a high level of purity.

The claimed method provided a polysaccharide preparation comprising 935 µg/mg of capsular polysaccharide from GBS serotype V and low amount of residual protein, nucleic acid and group B polysaccharide (see paragraph [00244], lines 56 to 57 and Table 24 of the patent).

The skilled person found, neither in D8 nor elsewhere, any incentive to remove the cationic detergent and its re-solubilisation steps to simplify the method of purifying a capsular polysaccharide from *S. agalactiae*. On the contrary, "[o]ne preferred method of preparing saccharides involves precipitation of the polysaccharide followed by solubilisation of the precipitated polysaccharide using a lower alcohol as described above. After re-solubilisation, the polysaccharide may be further treated to remove contaminants." (see page 12, lines 13 to 21). Hence, only after the polysaccharide was precipitated and re-solubilised was the polysaccharide preparation further processed to remove contaminants, which involved one or more steps of filtration, such as depth filtration, filtration through activated carbon may be used, size filtration and/or ultrafiltration. The activated carbon filtration was therefore inextricably linked to a polysaccharide precipitation and re-solubilization, whilst the method of claim 1 specifically excluded these steps.

There was no indication in this passage why the skilled person should turn to the activated carbon filtration and disregard the other proposed filtration options. There was no indication that the contaminants were specifically protein contaminants and not other contaminants, such as unwanted pigments (see document D8, page 11, lines 24 to 26).

Document D9 related to methods for removing excess soluble protein and other impurities from cellular lysates of *Streptococcus pneumoniae* (see page 1, lines 9-11). The process for producing purified capsular polysaccharides from a *Streptococcus pneumoniae* cell lysate comprised inter alia the steps of (a) to (f) and (g) where the clarified polysaccharide solution of step (f) was filtered through an activated carbon filter (see page 3 and 4). The method step (f) was carried out at least for 2 hours as well as overnight (see page 5, lines 1 to 2; page 6, lines 11 to 12; page 18, lines 21 to 23).

The capsular polysaccharides and the contaminants of *Streptococcus pneumoniae* and of the *Streptococcus agalactiae* were clearly different.

Whilst the skilled person could look to document D9 to find a solution to the problem of identifying a more simple process for purifying capsular polysaccharide from *Streptococcus agalactiae* that achieves a high level of purify they would not do so with the expectation of obtaining any improvement.

Firstly, the skilled person was aware that the yield obtained using the processes of document D9 was very poor (often as little as just 50%) and that the "purified" polysaccharides contained high levels of

impurities such as the C-polysaccharide (often as high as 25%). The carbon filtration step of document D9 resulted in a significant loss of polysaccharide yield whilst very little protein was removed. Even if the skilled person had attempted to combine the process of document D9 with that of document D8, the information and data in document D9 would have led him to dispense with carbon filtration altogether, thereby improving the yield by 20% without compromising purity.

The acidification step of document D9 was used to remove protein and performs precisely the same function as the step of alcoholic precipitation of the claimed method. These two steps are equivalent. Thus, if the skilled person was trying to simplify the purification process of document D8 by incorporating the acidification step, it would also have removed by the same token the step of alcoholic precipitation.

There was no incentive in documents D8 or D9 which would have motivated the skilled person to keep first the alcohol precipitation step, secondly have deleted the cationic detergent treatment and the subsequent re-solubilization of the method disclosed in document D8, and thirdly would have added a carbon filtration step of a method for purifying capsular polysaccharides from *S. pneumoniae* described in document D9, to arrive at the method of claim 1.

Thus, the claims were inventive in view of document D8 either alone or in combination with document D9.

XI. The submissions made by the **respondent**, insofar as relevant to the present decision, may be summarized as follows:

Main request (claims 1-14)
Article 123(2) EPC

There was no disclosure in the patent application of a method for conjugating a capsular polysaccharide (CPS) from *S. agalactiae* to a carrier protein comprising the method of any of claims 1 to 8 followed by conjugating the saccharide to a carrier protein according to claim 9. The paragraph [0142] of the patent application disclosed, at best, a protein carrier conjugated to a saccharide after the culture of bacteria and preparation of polysaccharide.

Admission of a new line of argument raised against the description under Article 123(2) EPC

First, the scope of examination in the notice of opposition was set out to cover Article 100 (a) to (c) EPC. An objection of added matter raised under Article 100(c) EPC was not a fresh ground of opposition which required appellant's consent to be admitted into the proceedings. The limitation set out in decision G 10/91 was accordingly not applicable. Reference was made to G 9/91 headnote.
Second, an objection under Article 123(2) EPC had been raised in opponent's notice of opposition under Article 123(2) EPC on page 4 last paragraph to page 5 referring to paragraphs [00161] to [00163] of the patent application. It mentioned that the scope of the adapted description of the patent was broader than that of the patent application as the specific *S. pneumococcus* had been replaced by the broader term *Streptococcus*.

Article 84 EPC

The method of claim 1 in step (iii) referred to a "filtration using a protein adherent filter which is an activated carbon filter immobilized in a matrix to which protein and DNA adheres but to which the capsular polysaccharide does not adhere". The patent provided no guidance on the conditions to be applied to the filter to bind proteins and DNA but not capsular polysaccharides. However, it was known that the binding of the proteins, DNA and polysaccharides to carbon filter were sensitive to the conditions used (see document D15 paragraphs [0066] and [0067]). Hence, it was unclear whether the DNA was eliminated by a carbon filtration step or by a previous or subsequent step (see paragraph [00185] of the patent).

Article 87 EPC

First, document P1 disclosed nowhere an activated carbon filter immobilized in a matrix. The passages in sections [0034] to [0035) of the patent application discuss matrix immobilized filter with no equivalent in document P1.

The starting material had to be "a crude isolate containing a capsular polysaccharides" (see claim 43 and paragraph [0033] of document P1). "The *Streptococcus* capsular polysaccharide obtained after culture", as described in paragraph [0106] following paragraphs [0101] to [0105] and paragraphs [0408] to [0410] of document P1, required a specific starting material which was not part of claim 1.

The application of a diafiltration step after a re-N-acetylation step as claimed in step (iv) and (v) of claim 1 was not disclosed in document P1. The step of of diafiltration was used after the precipitation of

proteins and/or nucleic acids, and before the detergent-mediated precipitation or filtration with a protein adherent filter (see paragraph [0113] of document P1).

The purification protocol reported in Example 6 starting on page 90 related to and used GBS type V polysaccharide and included a base treatment and a tangential diafiltration 30 kDa step that was missing in the method of claim 1 (see paragraphs [0407], [0409], [0417]).

Finally, claims 43 to 52 of document P1 included a step of cationic detergent treatment followed by a step of re-solubilization, explicitly excluded in the method of claim 1.

Thus, there was no direct and unambiguous link between the paragraphs recited by the appellant sufficient to support that the method of claim 1 was entitled to the priority right derived from document P1. For this reason claims 1 to 14 could not enjoy priority right from document P1.

Article 56 EPC

Document D8 represented the closest prior art.

It described methods that could be used for the preparation of the polysaccharides from GBS (see pages 8 to 13, especially page 8, lines 11 to 14). It further taught a purification process with the steps (i), (ii) and (iv) of claim 1:

(i) an alcoholic precipitation (see D8 page 9, 3rd paragraph et seq.);

(ii) a diafiltration (see D8 page 10, 4th paragraph et seq.) and
(iv) a re-N-acetylation (see D8 page 8, penultimate paragraph).

It disclosed furthermore that one of these methods involved polysaccharide precipitation followed by solubilisation of the precipitated polysaccharide using a lower alcohol as described above. After re-solubilisation, the polysaccharide was treated to remove contaminants. This was particularly important in situations where even minor contamination was not acceptable (e.g. for human vaccine production). Typically the process included a filtration step through activated carbon (see page 12, lines 13 to 21).

It established that the alcohol precipitation of contaminating proteins and/or nucleic acids allowed the capsular polysaccharides to remain in solution (see pages 9 to 10). The step of diafiltration could be used after the precipitation of proteins and/or nucleic acids, and before the detergent-mediated precipitation.

The difference between the method of claim 1 and document D8 was that the claimed method required a step (v) of diafiltration step, following the re-N-acetylation step (iv), and a step (iii) of filtration using a protein adherent filter which is an activated carbon filter. The method of claim 1 excluded a step of cationic detergent treatment to precipitate the capsular polysaccharide followed by a step of re-solubilization of the capsular polysaccharide.

Since the diafiltration after a re-N-acetylation step (iv) provided no surprising effect and was common in the art, especially in vaccine production, it could not

contribute to an inventive step. The step of re-solubilization was superfluous if no cationic precipitation had preceded.

Since no improvement was demonstrated for the process of claim 1 over the process of document D8, the objective technical problem ought to be defined as "the provision of an alternative process for purifying capsular polysaccharide from *S. agalactiae*".

Given that the process of claim 1 comprised at least five steps and could include many other steps, it was unclear why the claimed method was "a simpler process" than the ones described in document D8 (see e.g. Examples B and C of the patent).

The purity obtained using the process of Example B of the patent was calculated to be 93.5%, 75.7%, 74.6% and 78.5% for different serotypes (see last two lines of page 7 of the statement of the grounds of appeal, where 1000 µg/mg is considered to be 100% purity). Thus, the process of the patent could hardly provide for a method of purifying a capsular polysaccharide with an "improved" purity in which protein contaminants were removed.

The skilled person knew that when minor protein contaminants were not acceptable in a polysaccharide preparation (for example in vaccine production), activated carbon filters provided means to reduce them (see patent paragraph [0007] and [00232]).

First, since the starting material was not defined in claim 1, any purified material or material not obtained by base extraction or phosphodiesterase treatment, leading to capsular polysaccharide preparations

comprising group B contaminants, was a valid starting material (see e.g. page 10, lines 19 to 23). Having started with such a material, the skilled person would obviously have skipped the step of cationic detergent treatment and its subsequent re-solubilization step, as there was no need of removing group B contaminants. Finally, the skilled person was motivated to use an activated carbon filter to purify capsular polysaccharide at a high level of purity when even minor protein contaminants were not acceptable.

Document D9 described improved purification processes for *S. pneumoniae* polysaccharides and taught that the removal of impurities in the prior art was "spread over many labor intensive and costly steps. Protein level is the most problematic specification to meet due to the physical and chemical properties of the soluble proteins." (see D9 page 2, lines 20-23). Thus, there was a need for a simplified purification process to reduce the soluble protein levels in *S. pneumoniae* lysates and eliminate inefficiencies of the current purification process to produce substantially purified capsular polysaccharides suitable for incorporation into vaccines (see D9 page 2 lines 24-27). An activated carbon filter step was effective at removing protein contaminants (see page 4, line 3 to 5).
Reference was equally made to Example 3, entitled "Acidification and Activated Carbon Adsorption Step Efficiency Analysis (Serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, and 19F)", which reported that the most significant and important impurity to remove were the proteins. "Two of the major purification steps, acidification and activated carbon adsorption" were very efficient in that respect (see page 33, lines 17-19; Figs. 13 and 14; page 34, lines 8-10). The acidification and activated carbon adsorption steps

removed more than 98% and 90% protein, respectively (as measured by SDS-PAGE) (see page 34, lines 4 to 10; page 34, lines 25 to 27).
Even if the method related to the use of an acidification and a carbon filtration step, the acidification step was nowhere shown to affect the purification process of polysaccharides from GBS.
Document D1 related to harsh acidic conditions (2M acetic acid for 3h at 80°C; see page 1123, right column last paragraph), while document D15 did not relate to *Streptococcus* polysaccharides but related to *E. coli* lipopolysaccharides (LPS) (see paragraph [0004]).
Hence, neither document D1 nor document D15 provided evidence that an acidification step was detrimental to the purification of a capsular polysaccharides from *S. agalactiae*.

The process of claim 1 did not exclude an acid treatment step. Hence, the skilled person would not have disqualified the process described in document D9 because it included an acidification step. Since the patent application disclosed that polysaccharides from *Streptococcus* were purified in generic terms (see paragraphs [0038] to [0039]) and that the capsular polysaccharide of *S. agalactiae* and of *S. pneumoniae* comprise the same glycosyl groups, the skilled person would have adjusted the process of purification of the *S. pneumoniae* polysaccharides to the serotype to be purified.

As the starting material could be selected to comprise a capsular polysaccharide preparation whose group C antigen contaminant was absent or had been removed, the skilled person, faced with the technical problem of providing a simpler method than the method of document D8 would have ignored the cationic detergent

precipitation and its re-solubilization steps but would have kept the steps assigned to the removal of protein contaminants, i.e. the alcohol precipitation step, and would have added an activated carbon filter filtration step to lower even more the amount of residual protein contaminants.

Thus, the method of claim 1 lacked an inventive.

XII. The appellant requested that the patent be maintained on the basis of the main request or, in the alternative, on the basis of any of auxiliary requests 1 to 5 filed with its statement of grounds of appeal or, further alternatively, on the basis of auxiliary request 6 filed with its letter dated 20 December 2021.

XIII. The respondent requested that the appeal be dismissed.

Reasons for the Decision

Main request (claims 1-14)
Article 123(2) EPC

Admission of a new line of argument raised against the description under Article 123(2) EPC

1. In its response to the statement of grounds of appeal, the respondent raised for the first time in the proceedings an objection of added subject matter against a part of the description. This objection, to the extent that it is not based on facts already in the proceedings, constitutes an amendment of the subject-matter under discussion *vis-à-vis* the one brought forward in opposition proceedings.

2. According to the established case law, as reflected in Article 12(2) RPBA 2020, the function of an appeal is to review in a judicial manner the decision under appeal taken by an examining or opposition division. The admission of *inter alia* new lines of argument into the appeal proceedings is at the board's discretion and may be refused if it is concluded that these new lines of argument should have been presented or were not admitted during opposition proceedings (see Articles 114(2) EPC and 25(2) RPBA 2020 in conjunction with Article 12(4) RPBA 2007).

2.1 The respondent submitted that the objection raised against amendments to paragraphs [00161] to [00163] of the description under Article 123(2) EPC was neither a new line of argument nor a fresh ground requiring appellant's consent to be introduced into the proceedings, as set in decision G 10/91 (OJ EPO 1993, 420). The Opposition had *inter alia* been based on the ground set out in Article 100(c) EPC and the notice of opposition mentioned that the adapted description used broader terms than those of the paragraphs [00161] to [00163] it derived from. Thus in application of the principles established in decision G 9/91 (OJ EPO 1993, 408), the present board had the power to examine and decide on these submissions.

2.2 The board cannot agree with the respondent's view. Although the objection of added matter raised in the respondent's notice of opposition on page 4 and 5 explicitly mentions that the amended paragraphs of the description of the patent used broader terms than the corresponding paragraphs [00161] to [00163] of the patent application, these amended paragraphs were mentioned to highlight that the subject matter of claims 17 and 18 as granted had no direct and

unambiguous basis in the disclosure of the parent application. This interpretation is confirmed by the last sentence on page 5 of the notice of opposition, which states that claims 17 and 18 contravene Article 123(2) EPC for these additional reasons. Thus whereas in the board's view the limitations of G 10/91 do not apply in the present case, the principles expressed in G 9/91, referred to by the respondent, are of relevance.

2.2.1 Although the objection of added matter under Article 123(2) EPC raised in respondent's reply to the statement of grounds of appeal clearly relates to the same amended paragraphs [00161] to [00613] of the patent application, the conclusion that "[t]hese amendments add matter in the sense of Art. 123(2) and highlight the lack of basis in the original text of the parent application as filed, which provides no direct and unambiguous disclosure for the subject matter of claim 13." finds no support in the opponent's notice of opposition.

2.2.2 The objection under Article 123(2) EPC in the notice of opposition on page 5 focused on the subject-matter in claims 17 and 18. The amended paragraphs [00161] to [00163] of the description of the patent application merely supported this finding. There was no indication in the notice of opposition on page 4 or page 5 that the amended paragraphs [00161] to [00163] of the description of the patent themselves contravened the requirements of Article 123(2) EPC.

2.2.3 Thus, the respondent's line of argument that the amended paragraphs [00161] to [00163] of the patent application were contrary to the requirements of Article 123(2) EPC, and did not only serve to support

that claims 17 and 18 infringed Article 123(2) EPC, involves the consideration of new facts, which had not been discussed in opposition proceedings. The board sees no reason why this new line of argument was not brought forward during opposition, together with the other objections under Article 123(2) EPC, and does not consider that the appealed decision gave reason for filing it only in appeal proceedings.

2.2.4 For this reason, exercising its discretion under Article 12(4) RPBA 2007, the board decided not to admit this new line of argument under added subject-matter.

Article 123(2) EPC - claims 9-14

3. The board shares the view taken in the decision under appeal. Claim 9 relates to a method combining the method of any of claims 1 to 8 followed by the step of conjugating the saccharide to a carrier protein. This claim finds a basis in paragraphs [0036] and [0142] of the patent application.

3.1 Paragraph [0142] of the patent application relates to conjugate preparation. It mentions that "[A]fter culture of bacteria and preparation of capsular polysaccharides, the saccharide are conjugated to carrier protein(s)". This emphasises that a conjugation step can only take place if bacteria have been grown and capsular polysaccharides have been prepared beforehand. These earlier steps do not necessarily have to be part of a single method. This view is confirmed in paragraph [0036] of the patent application: "The starting material for the method of this aspect of the invention may be one of the starting materials described in the section entitled "Starting material" below." Thus, the sequence of steps of claim 1 may be

followed by a step or steps described in the section "Conjugate preparation". From this teaching the board finds that the culture of bacteria and the preparation of capsular polysaccharides and their conjugation to a carrier protein may, but need not, be combined.
Since any of the methods of claims 1 to 8 is not inextricably linked with a specific starting material, such as a cultured bacteria, the conjugation of the saccharide to the carrier following any one of the method of claims 1 to 8 does not offend Article 123(2) EPC.

3.2 The board notes that claim 1 was not objected to under Article 123(2) EPC. Claim 1 seems to find a basis in claims 43 to 48 and in paragraphs [0032] and [0034] of the patent application for preparing a capsular polysaccharide from *Streptococcus agalactiae.*
The resulting purified CPS from S. *agalactiae* may be, based on the rationale above, directly and unambiguously combined with a subsequent conjugation step to a carrier protein as disclosed in paragraph [0142] which results in a method as defined in claim 9.

3.3 The method of claim 13 further comprises the step of mixing individual conjugates prepared from one or more of Group B *Streptococcus* serogroups Ia, lb or III to provide a polyvalent mixture. The respondent contended that there was no basis for such a specific combination of features in the patent application.
The board shares the view taken in the decision under appeal with regard to claim 13 (see paragraph bridging pages 4 and 5 of the decision). Despite paragraphs [0161] and [0162] referring to pneumococci - which are not group B streptococci - the two next paragraphs begin with "For GBS, conjugates are preferably prepared from one or more of serogroups Ia, Ib or III." and

"[T]he conjugates may be mixed by adding them individually to a buffered solution (see paragraphs [0164] and [0165] of the patent application). Given the title of the section "Conjugate combinations" and the fact that GBS (i.e. *S. agalactiae*, see paragraph 4 of the patent) conjugates are prepared from one or more serogroups Ia, Ib or III (see paragraph [0164]), this paragraph alone discloses directly and unambiguously a mixture of CPS conjugates of one or more GBS serogroups Ia, Ib or III, independently of any buffered solution.

3.4 Thus, claims 9 to 14, and hence the main request, comply with the requirement of Article 123(2) EPC.

Article 84 EPC

The respondent contended that the method of claim 1 step (iii), referring to a "filtration using a protein adherent filter which is an activated carbon filter immobilized in a matrix to which protein and DNA adheres but to which the capsular polysaccharide does not adhere", was unclear. The method of claim 1 and the patent provided no guidance on the conditions to be applied to the filter to bind proteins and DNA but not capsular polysaccharides. The binding of the proteins, DNA and polysaccharides to carbon filter were known to be sensitive to the conditions used (see document D15 paragraphs [0066] and [0067]). Hence, it was unclear whether the DNA was eliminated by the carbon filtration step or by a previous or subsequent step (see paragraph [00185] of the patent).

3.5 First, the board notes that the method of claim 1 does not require elimination of the DNA during the filtration step (iii). It only requires that the carbon filter is capable of binding DNA to some extent, if at

all present, in the composition to be processed. The method of claim 1 does not exclude that DNA may be removed to some extent or completely from the composition to be purified in any previous or subsequent method steps. Thus, whether DNA was eliminated in previous or subsequent steps of the method is irrelevant to the clarity of the claimed method.

3.5.1 Second, claim 1 step (iii) relates to a filtration step using a structurally and functionally defined filter. There is no minimal purification degree to achieve. Thus, the skilled person can easily test and determine, using common general knowledge and standard techniques, whether a carbon filter under selected conditions binds both protein and DNA but not polysaccharides or not. The patent and document D15 confirm this view. Paragraph [0232] of the patent discloses how to remove residual protein contaminants when using a carbon filter, while paragraphs [0066] and [0067] of document D15 disclose how, in a process for purifying polysaccharides from *D. discoideum* and *N. meningitidis*, polysaccharides adsorbed to a carbon filter could be recovered by changing the buffering conditions. Thus, the functional language in step (iii) of the method of claim 1 is clear, and hence, the main request complies with Article 84 EPC.

Article 87 EPC

4. Pursuant to Article 87 EPC a European patent application enjoys a priority right only in respect of the *same invention* as was disclosed in the previous application. The *same invention* requirement, as interpreted by the established case law of the Boards of Appeal, means that priority of a previous

application in respect of a claim in a European patent application is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, explicitly or implicitly, using common general knowledge, from the previous application as a whole (see G 2/98, OJ EPO 2001, 413).

The board shares the view taken in the decision under appeal and of the respondent that no priority right can be validly claimed from document P1 (US61/008941) for the method of claim 1.

4.1 First, claim 1 does not define the starting material. It can be any starting material of any purity (not only crude isolates). In contrast, claims 43 to 52 and paragraph [0033] of document P1 require "a crude isolate containing a capsular polysaccharide as starting material (see claim 43 (a) and (b) of P1 and paragraph [0033] bridging pages 6 and 7, item (a) and (b) of document P1). Example 6 shows an exemplary purification protocol and discloses a starting material in the form of a fermented bacterial biomass that was treated with a base and then neutralized (see paragraphs [0408] to [0410]).

4.2 Second, claim 1 of the main request differs from claims 43 to 52 in document P1 at least in that:

- step (c) of claim 43: "filtering to remove smaller molecular weight compounds while retaining the capsular polysaccharide" is absent;
- claims 43 to 52 do not exclude a cationic detergent treatment followed by a step of re-solubilization, whereas claim 1 does;

- two diafiltration steps and in particular a diafiltration step (v) following step (iv) (re-N-acetylation) are missing.

4.3 Third, Example 6 paragraph [0417] of document P1 refers to a step wherein tangential diafiltration with a cut-off of 30kDa following a step (iv) of re-N-acetylation is conducted. A tangential diafiltration is not generalizable to any type of diafiltration step, as in claim 1 of the main request.

4.4 Fourth, the protocol of example 6 of document P1 comprises two additional specific steps:
- treating the fermented bacterial biomass with a base and neutralizing it - so as to release the CPS into the supernatant - and
- recovering the supernatant from an alcohol precipitation by tangential microfiltration.

4.5 Example 6 of document P1 comprises method steps that are either more or less specific than the corresponding steps of the method of claim 1. First, it comprises two tangential diafiltration steps with a 30kDa membrane cut-off, second an alcohol precipitation step in the presence of $CaCl_2$, and third, an in-depth filtration on a CUNO Biocap 2000 1300 cm^2 capsule.

4.6 For these reasons the method of Example 6 of document P1 does neither explicitly disclose the method of claim 1 nor can the skilled person, on account of the common general knowledge, derive the method of claim 1 directly and unambiguously from Example 6.

4.7 Even considering the specific paragraphs of document P1 highlighted by the appellant, the skilled person would

not have directly and unambiguously derived therefrom the method as defined in claim 1.

4.7.1 Paragraphs [0033] to [0036] of document P1 relate to one or more of the following steps (a) to (d).

- Both steps (a) and (b) refer to a crude isolate [containing a capsular polysaccharide], while claim 1 does not.
- Step (b) refers to contacting the crude isolate with an alcohol solution, in certain embodiments most preferably comprising calcium (see [0035]), while claim 1 refers to an alcohol solution comprising a divalent cation.
- Step (c) relates to filtering to remove smaller molecular weight compounds while retaining the capsular polysaccharide, while claim 1 refers to diafiltration.
- Step (d) relates to removing protein contaminants with a protein adherent filter to produce the purified capsular polysaccharide, in certain embodiments an activated carbon filter ([0036]), while claim 1 refers to an activated carbon filter immobilised in a matrix to which protein and DNA adheres but to which the capsular polysaccharide does not adhere.

In a preferred embodiment, the method includes all of the foregoing steps. In a more preferred embodiment, the method omits detergent precipitation.
In certain embodiments, one or more additional steps may be performed including (e) re N-acetylating the purified capsular polysaccharide.

4.7.2 Paragraphs [0106] to [0112] of document P1 relate to alcoholic precipitation and cation exchange, wherein divalent cations are particularly preferred and wherein the alcohol mixture preferably includes calcium ion.

Paragraph [0113] of document P1 relates to diafiltration, which may be used before the detergent-mediated precipitation or filtration·with a protein adherent filter. Tangential flow diafiltration is typical.
Paragraph [0116] of document P1 relates to polysaccharide precipitation using one or more cationic detergents, though preferred embodiments of the purification will exclude detergent precipitation.
Paragraph [0127] relates to filtration with a protein adherent filter preferably being a carbon filter.
Paragraph [0103] relates to the polysaccharide preparation and mentions that re-N-acetylation may be necessary as an earlier base treatment de-N-acetylates the capsular saccharide.

4.7.3 The priority application P1 neither explicitly nor implicitly yet directly and unambiguously discloses the combination of steps and features defined in claim 1. Thus, the claims of the main request do not enjoy priority rights from document P1 and document D9 is relevant prior art under Article 54(1)(2) EPC.

Article 56 EPC

The closest prior art

5. It is common ground between the parties that document D8 represents the closest prior art for the subject-matter of claim 1.

5.1 Group B Streptococcus or *S. agalactiae* is known as GBS (see paragraph [0004] of the patent).

5.2 Document D8 discloses a method for purifying capsular polysaccharide, preferably from GBS (see page 2, line

13). "For GBS, the following methods may be used" (see page 8, line 14) which are described in further detail on pages 8 to 12.

- an alcoholic precipitation (preferably with divalent cations);
- a diafiltration,
- a cationic detergent treatment and
- a carbon filtration following the step of detergent mediated precipitation and resolubilization (see section "re-solubilization").

Although the starting material for alcoholic precipitation may be the supernatant of a centrifuged bacterial culture, in which a small amount of capsular polysaccharide is released during bacterial culture, more typically, it is prepared by treating the bacteria themselves, such that the capsular saccharide is released, by chemical, physical or enzymatic treatment prior to the initial protein/nucleic acid precipitation reaction. A preferred starting material is obtained by base extraction or by type II phosphodiesterase (PDE2) treatment of *Streptococcus* (see page 8, penultimate paragraph to page 9, first full paragraph).

Streptococcus capsular saccharide obtained after culture is known to be impure and contaminated with bacterial nucleic acids and proteins. These contaminants can be removed either by RNase, DNase and protease treatment or alternatively by alcoholic precipitation. When the starting material is obtained by base extraction it usually needs to be neutralised.

The final concentration of alcohol is one that achieves adequate precipitation of contaminants without precipitating the polysaccharide. It preferably

contains calcium chloride. After alcohol precipitation, the precipitated material can be separated from the polysaccharide by any suitable means (see page 9, 2nd full paragraph to page 10, 4th paragraph).

The step of diafiltration may be used after the precipitation of proteins and/or nucleic acids, and before the detergent-mediated precipitation. This step is particularly advantageous if base extraction or phosphodiesterase has been used for the release of the capsular saccharide (see page 10, 4th paragraph).

The cationic detergent treatment precipitates the capsular saccharide and advantageously and conveniently minimises contamination by group-specific saccharide from the partially purified capsular polysaccharide from *Streptococcus* (see page 11, first paragraph). The polysaccharide precipitate can be re-solubilised in aqueous medium or in alcoholic medium depending on the residual contaminants present at this stage. Pigments can effectively be removed by alcoholic re-solubilisation followed by carbon filtration (see page 11, 4th paragraph, especially lines 24 to 26).

Finally, one preferred method for preparing the saccharides involves "polysaccharide precipitation followed by solubilisation of the precipitated polysaccharide using a lower alcohol as described above. After re-solubilisation, the polysaccharide may be further treated to remove contaminants. This is particularly important in situations where even minor contamination is not acceptable (e.g. for human vaccine production)" (see page 12, lines 13 to 21).

5.3 According to the respondent, the difference between the methods of document D8 and the method of claim 1 was

that the claimed method required a diafiltration step following the re-Nacetylation step, and a step (iii) of filtration using a protein adherent filter which is an activated carbon filter. Furthermore, the method of claim 1 excluded a cationic detergent treatment to precipitate the capsular polysaccharide followed by a step of re-solubilization of the capsular polysaccharide.

5.4 Considering the above differences, the respondent did not agree to define the technical problem as "a more simple process for purifying capsular polysaccharide from *S.agalactiae* that achieves a high level of purity" as claim 1 "comprised" but was not limited to the steps defined in claim 1.

5.5 The board notes that the method according to claim 1 is defined by both its purpose and its essential steps (i) to (v).
The method according to claim 1 differs from the method described in document D8 in that it includes a step of filtration using an activated carbon filter immobilized in a matrix, while it excludes a step of cationic detergent treatment and re-solubilization.

5.6 The board notes that the method of claim 1 fails to define the starting material of the purification process (see also point 4.1 above). In this context, document D8 mentions that capsular polysaccharides need to be re-N-acetylated after base treatment (see page 8, lines 26 to 27). However, if the capsular polysaccharides of *S. agalactiae* are released by a process other than base extraction, steps (iv) and (v) are not expected to have any technical effect and thus cannot contribute to an inventive step.

5.7 Since, the method for purifying a capsular polysaccharide from *Streptococcus agalactiae* comprising steps (i) to (v) excludes a step of cationic detergent treatment and re-solubilization comprised in the process disclosed in document D8, the board concludes that the claimed method is simpler than method the method described in document D8.
This simplification may not only be achieved by reducing the number of steps, but also by making the claimed process faster, less cumbersome and time-consuming than the method described in document D8.
Hence, the technical problem may be defined as a simpler method of purifying a capsular polysaccharide from S. agalactiae.

5.8 The respondent contended that this problem was not solved.

5.9 The board agrees with the respondent's objection that there is no evidence that the results shown in Table 20 of the patent were obtained by the purification process of claim 1. However, this conclusion does not extend to the purification method used in Example B and Table 24 of the patent, which reports 93.5%, 75.7%, 74.6% and 78.5% for the different serotypes respectively. The method according to claim 1 provides a capsular polysaccharide preparation with a high level of purity.

The claimed method need not result in an improved degree of purity, as argued by the respondent. Being effective at removing contaminants is sufficient.

5.10 Thus, in the light of Example B and Table 24, the board is satisfied that the underlying technical problem is solved by the method of claim 1.

Obviousness

5.11 Hence, the sole issue that remains to be decided is whether or not starting from the methods of document D8, a skilled person, faced with the technical problem identified above, would have modified the methods to arrive at a method according to claim 1 in an obvious manner.

5.11.1 The board is not convinced that this is the case.

First, document D8 refers to contaminants in general and not to protein contaminants.

5.11.2 Second, removal of contaminants in document D8 is described for one preferred method for preparing the saccharides (see page 12, lines 13 to 21). This method involves the step of polysaccharide precipitation followed by solubilization of the polysaccharide precipitate using alcohol, wherein after re-solubilization the polysaccharide can be further treated to remove contaminants. Such further steps are described on page 11, paragraphs 1 to 5. Cationic detergents are used for the polysaccharide precipitation, while the polysaccharide precipitate must subsequently be re-solubilised.

5.11.3 Third, filtration through activated carbon is just one of several filtration steps mentioned on page 12.

5.12 On page 12, it is stated that one preferred method of purifying *S. agalactiae* may further involve one or more steps of filtration e.g. depth filtration, filtration through activated carbon, size filtration and/or ultrafiltration, when even minor contamination is not acceptable (e.g. for human vaccine production). This

preferred method however explicitly involves a step of polysaccharide precipitation by detergent followed by a step of solubilisation of the precipitated polysaccharide, steps which are excluded from the method of claim 1.

5.12.1 Thus, starting from the preferred method of document D8, the skilled person, faced with the technical problem identified above, has no reason and motivation to skip the step of polysaccharide precipitation followed by solubilisation of the precipitated polysaccharide in order to arrive at the claimed method.

5.13 Even if, arguendo, the skilled person started with another method for purifying capsular polysaccharide from *S. agalactiae* disclosed in document D8, it would have selected the preferred starting material obtained by base extraction or enzymatic PDE2 treatment (see page 9, first full paragraph). However, these starting materials release group-specific saccharide, to give fragments much smaller than the intact capsular saccharide (see page 10, lines 20 to 23). Thus, the skilled person faced with the technical problem identified above and using the preferred starting material of document D8 had no incentive to skip the step of polysaccharide precipitation by cationic detergent followed by solubilisation of the precipitated polysaccharide either.
Even if document D8 mentions that for GBS preparation and purification the following methods (plural form) may be used, the board finds no hint or motivation to perform a method for purifying capsular polysaccharide from *S. agalactiae* specifically involving the steps of an alcoholic precipitation and cation exchange, diafiltration and filtration using an activated carbon

filter binding protein and DNA but explicitly excluding a cationic detergent treatment and a re-solubilization step.

5.13.1 Thus, based on the disclosure of document D8 alone, the claimed method is not obvious.

5.14 This conclusion does not change even if document D8 is considered in combination with document D9.
Document D9 discloses a process for purifying capsular polysaccharides from a cellular *Streptococcus pneumoniae* lysate broth. The process comprises ultrafiltering and diafiltering a clarified *S. pneumoniae* lysate followed by pH adjustment to less than 4.5 and filtration using activated carbon (see e.g. D9 page 3, lines 2 to 27). The process does not include a step of cationic detergent treatment to precipitate the capsular polysaccharide.

5.15 The patent application contemplates a method of purifying capsular polysaccharides from *Streptococcus. Streptococcus* genus includes *S. pneumoniae*. Even if document D9 describes a method of purifying a capsular polysaccharide from *S. pneumoniae* and, in one embodiment, an activated charcoal filter step (g) was effective in removing protein contaminants, there is no evidence in document D9 that the method of purifying capsular polysaccharides comprising a step of using a protein-adherent filter which is an activated charcoal filter immobilised in a matrix is applicable to other species of Streptococcus, such as *S. agalactiae*. Although the capsular polysaccharide purification of *S. agalactiae* and *S. pneumoniae* include the same glycosyl groups, the preparations to be purified comprise different protein and polysaccharide contaminants.

5.16 The board agrees with the respondent that an acidification step, as carried out in document D9, is not excluded in the method of claim 1. Example C of the patent confirms this analysis (see paragraph [00254] and claims 3 and 5 of the patent). Hence this step cannot constitute a meaningful difference.

5.17 The board considers that starting from document D8 the skilled person, faced with the objective technical problem of providing a simplified method for purification of capsular polysaccharide from *S. agalactiae* with a high level of purity, could have applied an activated carbon filter effective at removing protein contaminants as described in document D9, but would have kept the acidification step preceding the carbon filtration step, which was even more efficient at removing protein contaminants (see Figure 13). The skilled person would concomitantly have deleted the superfluous alcohol precipitation step of the method of document D8 in order to simplify it.

5.18 Therefore, the specific sequence of steps of the claimed method cannot be considered obvious for the skilled person in the light of the teaching of document D8 either alone or in combination with document D9, which relates to methods for removing excess soluble protein and other impurities from cellular lysates of *Streptococcus pneumoniae*.

6. In view of the above, the board concludes that the method of claim 1 of the main request involves an inventive step. The same applies to dependent claims 2 to 14.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in accordance with claims 1 to 14 of the main request filed with the statement of the grounds of appeal and a description to be adapted.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated