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Datasheet for the decision of 20 December 2006

Case Number: T 0348/05 - 3.3.03

Application Number: 92300655.5

Publication Number: 0497525

IPC: A61K 39/385

Language of the proceedings: EN

Title of invention:
Pneumococcal polysaccharide conjugate vaccine

Patentee:
Merck & Co., Inc.

Opponent:
SmithKline Beecham Biologicals SA

Headword:
-

Relevant legal provisions:
EPC Art. 54, 83, 84, 100(a), 100(b), 100(c), 111(1), 123(2), 123(3)
RPBA Art. 10b, 10b(1)

Keyword:
"Sufficiency of disclosure (yes)"
"Late filed request - admitted"
"Error of judgement - procedural violation (no)"
"Remittal"

Decisions cited:
G 0009/91, T 0301/87

Catchword:
-

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Case Number: T 0348/05 - 3.3.03

D E C I S I O N
of the Technical Board of Appeal 3.3.03
of 20 December 2006

Appellant: (Patent Proprietor)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office dated 16 April 2003 and posted 18 January 2005 revoking European patent No. 0497525 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: R. Young
Members: C. Idez
E. Dufrasne

Summary of Facts and Submissions

I. The grant of the European patent No. 0 497 525 in the name of Merck & Co. Inc. in respect of European patent application No. 92 300 655.5 filed on 27 January 1992 and claiming priority of the US patent application No. 646570 filed on 28 January 1991 and of the US patent application No. 807942 filed on 19 December 1991 was announced on 19 August 1998 (Bulletin 1998/34) on the basis of 9 claims.

Claims 1 to 4, and 6 to 9 read as follows:

"1. A conjugate comprising an immunogenic protein covalently linked to a polysaccharide derived from one or more subtypes of Streptococcus pneumoniae, said polysaccharide having, on average, less than about 1200 repeating units per molecule, a molecular weight between 1 x 10^5 and 1 x 10^6, a polydispersity between 1.0 and 1.4, and a level of contamination by pneumococcal group-specific C-polysaccharide below 3.0% of the type-specific polysaccharide.

2. The conjugate of Claim 1 wherein said polysaccharide has an antigenicity index between 0.7 and 1.1, and an intrinsic viscosity between 0.6 and 3.0 dL/g.

3. The conjugate of Claim 2 wherein said polysaccharide is derived from any of the subtypes of Streptococcus pneumoniae selected from: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F.

4. The conjugate of Claim 3 wherein said polysaccharide is derived from:

1) Streptococcus pneumoniae 6B, said polysaccharide having:
a) a M_N between 3×10^5 and 6×10^5;
b) a K_d (peak) of about 0.60 ± 0.05;
c) a M_W between 3×10^5 and 7×10^5;
d) an intrinsic viscosity in 0.1 M sodium phosphate, pH 7.2, between 1.0 and 2.0; and
e) less than about 1000 repeating units per molecule on average;

2) Streptococcus pneumoniae 14, said polysaccharide having:
a) a M_N between 3×10^5 and 8×10^5;
b) a K_d (peak) of about 0.60 ± 0.05;
c) a M_W between 4×10^5 and 1×10^6; and
d) an intrinsic viscosity in 0.1 M sodium phosphate, pH 7.2, between 0.6 and 1.6;

3) Streptococcus pneumoniae 19F, said polysaccharide having:
a) a M_N between 2×10^5 and 6×10^5;
b) a K_d (peak) of about 0.65 ± 0.05;
c) a M_W between 2×10^5 and 6×10^5;
d) an intrinsic viscosity in 0.1 M sodium phosphate, pH 7.2, between 1.0 and 2.0; and
e) less than about 1000 repeating units per molecule, on average;

4) Streptococcus pneumoniae 23F, said polysaccharide having:
a) a M_N between 2×10^5 and 6×10^5;

b) a K_d (peak) of about 0.54 ± 0.05;
c) a M_W between 4 x 10^5 and 8 x 10^5;
d) an intrinsic viscosity in 0.1 M sodium phosphate, pH 7.2, between 1.5 and 3.0; and
e) less than about 1000 repeating units per molecule, on average,

5) Streptococcus pneumoniae 4, said polysaccharide having:
a) a M_N between 2 x 10^5 and 4 x 10^5;
b) a K_d (peak) of about 0.65 ± 0.05;
c) a M_W between 2 x 10^5 and 5 x 10^5;
d) an intrinsic viscosity in 0.1 M sodium phosphate, pH 7.2, between 1.0 and 3.0; and
e) less than about 600 repeating units per molecule, on average;

6) Streptococcus pneumoniae 9V, said polysaccharide having:
a) a M_N between 3 x 10^5 and 6 x 10^5;
b) a K_d (peak) of about 0.65 ± 0.05;
c) a M_W between 3 x 10^5 and 7 x 10^5;
d) an intrinsic viscosity in 0.1 M sodium phosphate, pH 7.2, between 1.0 and 2.0; and
e) less than about 800 repeating units per molecule, on average;

7) Streptococcus pneumoniae 18C, said polysaccharide having:
a) a M_N between 2 x 10^5 and 6 x 10^5;
b) a K_d (peak) of about 0.65 ± 0.05;
c) a M_W between 2 x 10^5 and 6 x 10^5;
d) an intrinsic viscosity in 0.1 M sodium phosphate, pH 7.2, between 1.5 and 3.0. and

e) less than about 700 repeating units per molecule, on average;

or a mixture of any of these polysaccharides; wherein said polysaccharide is conjugated to the outer membrane protein complex (OMPC) of Neisseria meningitidis b, or the MIEP subunit thereof.

6. A pneumococcal polysaccharideimmunogenic protein conjugate produced by the process of:
(a) Culturing a pneumococcus and isolating crude pneumococcal polysaccharide or solubilizing pneumococcal polysaccharide powder;
(b) Purifying and partially-hydrolyzing the polysaccharide of step (a) to an endpoint predetermined to generate a polysaccharide amenable to conjugation having no more than a 30% reduction of the polysaccharide's type-specific antigenicity as compared with the crude polysaccharide of step (a); and
(c) Conjugating the product of step (b) with an immunogenic protein, wherein the pneumococcus cultured in step (a) is selected from one or more of the subtypes: 4, 6B, 9V, 14, 18C, 19F, and 23F,wherein the Pn-Ps retains its antigenic integrity as measured by Ouchterlony double immunodiffusion or rate nephelometry assay using an anti-Pn-Ps type-specific antibody, said Pn-Ps prior to conjugation being physically sheared in a Gaulin press at a pressure between about 13.8 MPa and 103 MPa (2000 and 15000 PSI) or hydrolyzed by heating at 100°C for 24 hours or by sonicating, to a viscosity for a 1 mg/ml solution in 0.9 M sodium chloride or Kd (peak) endpoint as follows for each listed Pn-Ps subtype:

Pn-Ps Subtype	Target Endpoint Viscosity (centistokes)	Target Endpoint K_d (peak)
Pn4-Ps	1.5 - 1.00	0.65 ± 0.05
Pn6B-Ps	1.3 - 1.00	0.60 ± 0.05
Pn9V-Ps	1.3 - 1.00	0.65 ± 0.05
Pn14-Ps	1.1 - 0.95	0.60 ± 0.05
Pn18C-Ps	1.5 - 1.00	0.65 ± 0.05
Pn19F-Ps	1.3 - 1.00	0.65 ± 0.05
Pn23F-Ps	1.5 - 1.00	0.54 ± 0.05;

optionally followed by chromatographic or alcohol fractionation to select material having a polydispersity below 1.4.

7. A process for making a Pn-Ps-PRO conjugate which comprises:
a) Isolating crude pneumococcal polysaccharide, Pn-Ps;
(b)
1-Optionally, adsorbing onto Whatman DE52 anionic impurities at a solution pH of about 5;
2-Partially hydrolyzing the Pn-Ps in solution to an endpoint viscosity predetermined to diminish the Pn-Ps binding to anti-pneumococcal type specific antibody by no more than 30% as compared with crude Pn-Ps by:

1. heating at 50 to 150°C for between 1 to 48 hours; or
2. sonicating for periods of 5 seconds to 5 minutes, depending on the power setting of the sonication probe, followed by periods of cooling and additional sonication; or
3. shearing in a Gaulin press at pressures between about 13.8 MPa and 103 MPa (2000 and 15000 PSI);

(c) Fractionating the hydrolyzed Pn-Ps and selecting a fraction having a molecular weight in the range between $1x10^5$ and $1x10^6$ by:
i-differential alcohol solubility using isopropanol at concentrations predetermined to precipitate the desired Pn-Ps size range, or
ii-fractionation on a size-exclusion liquid chromatography column capable of including and fractionating polysaccharides in the size range between $5x10^4$ and $1x10^6$, and the endpoint for hydrolysis or shear is determined by viscometry of a 1 mg/ml solution in 0.1 M sodium phosphate, pH 7.2, or chromatography for each of the listed polysaccharides according to the end-point for that subtype Pn-Ps:

Pn-Ps Subtype	Target Endpoint Viscosity (centistokes)	Target Endpoint K_d (peak)
Pn4-Ps	1.5 - 1.00	0.65 ± 0.05
Pn6B-Ps	1.3 - 1.00	0.60 ± 0.05

Pn-Ps Subtype	Target Endpoint Viscosity (centistokes)	Target Endpoint K_d (peak)
Pn9V-Ps	1.3 - 1.00	0.65 ± 0.05
Pn14-Ps	1.1 - 0.95	0.60 ± 0.05
Pn18C-Ps	1.5 - 1.00	0.65 ± 0.05
Pn19F-Ps	1.3 - 1.00	0.65 ± 0.05
Pn23F-Ps	1.5 - 1.00	0.54 ± 0.05.

d) Derivatizing the fractionated Pn-Ps, derived from one or more pneumococcal subtypes according to steps (a)-(c), to display pendant nucleophilic or electrophilic moieties;
e) Isolating Neisseria meningitidis b 0MPC, or subunits thereof;

f) Functionalizing the OMPC or subunit thereof to exhibit reactive electrophilic or nucleophilic moieties;
g) Conjugating the polysaccharide of step (d) with the protein of step (f);
h) Capping the conjugate to remove residual functional groups;
i) Isolating the conjugate product.

8. The use of the conjugate of Claim 1 for the manufacture of a medicament adapted for immunisation against disease states attributable to pneumococcal pathogens.

9. A vaccine composition comprising the conjugate of Claim 1 and an inert carrier, and optionally comprising immunologically effective amounts of adjuvant or immunomodulatory compounds or additional immunogens wherein said inert carrier is aluminum hydroxide, aluminum phosphate, alum, and wherein said additional immunogens are selected from among one or more of the vaccines against hepatitis B, hepatitis A, non-A non-B hepatitis, AIDS, diptheria-pertussis-tetanus, measles, mumps, rubella, varicella, polio, and Haemophilus influenzae b, wherein the conjugate comprises between one and all of the conjugates selected from Pn4-Ps-OMPC, Pn6B-Ps-OMPC, Pn9V-Ps-OMPC, Pn14-Ps-OMPC, Pn18C-Ps-OMPC Pn19F-Ps-OMPC, Pn23F-Ps-OMPC, Pn1-Ps-OMPC, Pn5-Ps-OMPC, and Pn7F-Ps-OMPC.

Claim 5 was dependent on Claim 4.

II. On 19 May 1999, a Notice of Opposition was filed against the patent by SmithKline Beecham Biologicals SA

in which revocation of the patent in its entirety was requested on the grounds of lack of novelty and lack of inventive step (Article 100(a) EPC) and on the ground of insufficiency of disclosure (Article 100(b) EPC).

The following documents have been *inter alia* cited in the course of the opposition proceedings:

L1: B. Bednar et al. "Molecular size analysis of capsular polysaccharide preparations from *Streptococcus pneumoniae*", Carbohydrate Research, Vol. 243, 1993, pages 115-130;

L2: S. Harding et al. "Molecular weight determination of polysaccharides", Advances in Carbohydrate Analysis; Volume 1, 1991, pages 63-144;

L5: Declaration of Dr Jean Smal dated 18 September 2002; and

L6: Declaration of Dr Jean Smal dated 12 February 2003.

III. By a decision announced orally on 16 April 2003 and issued in writing on 18 January 2005, the Opposition Division revoked the patent.

The decision of the Opposition Division was based on a main request as submitted with letter dated 13 February 2003 of the Patent Proprietor and on two auxiliary requests as submitted during the oral proceedings of 16 April 2003.

According to the decision, Claim 1 of the main request infringed Article 123(3) EPC, and did not meet the requirements of Article 84 EPC.

The first auxiliary request was refused because Claim 1 thereof did not meet the requirements of Article 123(2) EPC. Concerning the second auxiliary request it was held in the decision that it met the requirements of Articles 123(2), 123(3), 84 and 54 EPC, but that it did not fulfil the requirements of Article 83 EPC, since the obtaining of the partition coefficient K_d range and the obtaining of the intrinsic viscosity range recited in Claim 1 were not enabled.

IV. A Notice of Appeal was filed on 17 March 2005 by the Appellant (Patent Proprietor) with simultaneous payment of the prescribed fee.

V. With the Statement of Grounds of Appeal filed on 27 May 2005, the Appellant filed a new main request and eight auxiliary requests, as well as, *inter alia*, the following documents:

Curriculum Vitae of Dr G. Berth;
and L12: Declaration of Dr G. Berth, dated 26 May 2005.

It also submitted arguments concerning sufficiency of disclosure, which may be summarized as follows:

(i) The fundamental issue in relation to insufficiency was that the Opponents had nowhere demonstrated that the skilled person could not reproduce the claimed invention. The burden of proof in this matter was on the Opponents.

(ii) The Opposition Division was incorrect to focus on the details of measuring parameters.

(iii) The Opposition Division had found that the skilled person could not measure the parameter K_d on the basis of the disclosure of the patent since there was no indication of what buffer system should be used.

(iv) The specification provided the skilled person with the general guidance on the measurement of K_d on page 4. Exemplary temperatures, standards, sample and injection volumes, Vo/Vi ratios and standard K_d values were also given.

(v) It would have been within the technical capabilities of the skilled person to select an appropriate chromatography column which would enable the measurement of K_d within the values indicated in the claims.

(vi) There would also have been no difficulty for the skilled person to select an appropriate buffer system when measuring K_d.

(vii) As explained in the declaration of Dr. Berth (L12), a buffer system was needed when measuring the partition coefficient of polysaccharides dissolved in water in order to suppress polyelectrolyte effects. This was part of the common general knowledge of the skilled person.

(viii) Since the variation in the amounts of buffer giving good effects was fairly small, i.e. in the range

of 0.05 and 0.2 M, there would be no undue burden on the skilled person to find an appropriate amount on a case-by-case basis.

(ix) Furthermore, if the amount of buffer was varied, within appropriate amounts, similar values of K_d would be obtained.

(x) An exemplary amount of buffer was provided in Example 30 at page 42, line 13 where 0.2 M sodium acetate was used.

(xi) The Opposition Division had found that a reproducible method for measuring the intrinsic viscosity was not disclosed, since there was no disclosure concerning the concentration values of polysaccharide which should be used to extrapolate this value.

(xii) The fact that methods were disclosed in the specification on pages 4 and 5 as to how intrinsic viscosity could be measured was evidence that it was within the common general knowledge of the skilled person to do so.

(xiii) The Patent Proprietor had proposed a method based on the size exclusion chromatography (SEC) method described. The Opposition Division had considered that this method was insufficiently described due to the absence of information concerning the concentration of analyte loaded into the column.

(xiv) This was however part of the common general knowledge of the skilled person.

(xv) The precise measuring conditions for a well-known parameter did not affect the reproducibility of the invention. The mere fact that differing values might be obtained would be an issue for Article 84 EPC not Article 83 EPC.

(xvi) According to Dr Berth's declaration methods of measuring intrinsic viscosity were well within the capabilities of the skilled reader. In particular, it was conventional, and convenient, to choose a highly dilute solution of a polysaccharide in order to obtain an acceptable approximate value of intrinsic viscosity.

VI. With its letter dated 7 October 2005, the Respondent (Opponent) submitted the following documents:

L9: Declaration of Dr Stephen Harding dated 7 October 2005, and

L10: Declaration of Dr Jean Smal dated 7 October 2005.

It also presented arguments concerning sufficiency of disclosure which may be summarized as follows:

(i) If a patentee had defined a product through the use of parameters, then in order for a skilled person to be able to follow the teaching of the specification he must be able to accurately measure the parameter as intended by the patentee in order to be able to make the precise product that was intended to be claimed.

(ii) Concerning the intrinsic viscosity parameter, a skilled person must know the concentration of the

polysaccharide used for the determination of the intrinsic viscosity.

(iii) Intrinsic viscosity varied considerably with respect to concentration.

(iv) Unless the skilled person was sure that he was measuring the parameter in the precise way intended by the patentee, he could never be sure that he had made the product claimed.

(v) Consequently, the product claimed could not be described in a manner sufficiently clear and complete for it to be made by the skilled person.

(vi) Concerning K_d the recitation of buffer conditions was essential for the skilled person to use this parameter properly to know he had made the claimed product (cf. also document L10).

(vii) The Patent Proprietor had given no guidance as to which temperature viscosity measurements which were meant to define the claimed population of polysaccharides should be carried out at.

(viii) Viscosity was highly dependent on temperature (cf. L9 and L10).

(ix) The skilled person would not be able to reproduce a particular polysaccharide population with certainty if it was defined only with reference to a viscosity value without reference to temperature.

VII. With its letter dated 2 November 2005, the Respondent submitted the following documents:

L10b: Declaration of Dr Jean Smal dated 25 October 2005, and

L11: X. Guo et al. "Determination of molecular weight of heparin by size exclusion chromatography with universal calibration"; Analytical Biochemistry Vol. 312 (2003), pages 33-39.

VIII. In a communication dated 9 October 2006, annexed to the Summons to Oral Proceedings scheduled to take place on 20 December 2006, the Board presented its provisional view on points concerning the allowability of the requests then on file under Article 123(2), 123(3) and 84 EPC, the determination of the partition coefficient K_d, the intrinsic viscosity and the target end-point viscosity, the use of the universal calibration method for determining the molecular weight and the polydispersity of capsular polysaccharides, and the compliance of the decision under appeal with the requirements of Article 113 (1) EPC in view of the apparent admission of the ground of opposition according to Article 100(c) EPC into the opposition proceedings.

IX. In its letter dated 17 November 2006, the Respondent essentially relied on its previous submissions.

Concerning the introduction of the ground of opposition according to Article 100(c) EPC, it was argued that no concern had been expressed in that respect by the Patent Proprietor in its Statement of Grounds of

Appeal. It hence did not seem that it had had reservation on the admission of that ground.

X. With its letter dated 20 November 2006, the Appellant submitted a new main request and five auxiliary requests, as well as the following documents:

L19: Second declaration of Dr Gisela Berth dated 17 November 2006;

L20: Declaration of Dr Michael Gentzler dated 16 November 2006.

The Appellant argued essentially as follows:

(i) Admission of the ground of opposition according to Article 100(c) EPC:

(i.1) There had been no discussion of the admissibility of this ground at the Oral Proceedings of the Opposition Division.

(i.2) There had certainly been no presentation in writing of the introduction of this ground and the essential legal and factual reasons which would substantiate it.

(i.3) Consequently the Patent Proprietor was not fully informed of the case to be met at the Oral Proceedings, and it was hence unable to present comments on the admissibility of this ground, as required by Article 113(1) EPC.

(i.4) In view of this substantial procedural violation, this portion of the decision should be set aside and reimbursement of the appeal fee be warranted assuming the Patent Proprietor would succeed on the other issues in this appeal.

(ii) Concerning sufficiency of disclosure:

(ii.1) As shown in document L20 intrinsic viscosity of the polysaccharides of the invention was practically the same when measured at temperatures between 20 and 25°C.

(ii.2) This issue had been raised in a Summons to Oral Proceedings deemed to be received exactly two months before the Oral Proceedings. Very limited time had been provided for the Appellant to produce data to prove a point in their favour which was never previously argued against them.

(ii.3) In the absence of alternative information in the specification, the skilled person would assume that intrinsic viscosity should be measured at room temperature (i.e. in a range of 20-25°C).

(ii.4) The temperature data provided by the Respondent in L9 and L10 related to end-point viscosities, not to intrinsic viscosities.

(ii.5) The skilled person would assume that intrinsic viscosity should be measured in water.

(ii.6) The Patent Proprietor had never stated that the skilled person would measure intrinsic viscosity in any medium other than water.

(ii.7) The actual reason why the Opposition Division held intrinsic viscosities to be insufficiently disclosed was because they believed them to be concentration dependent. This was, however, wrong.

(ii.8) The skilled person had a number of methods available for measuring intrinsic viscosity. One method involved taking a single measurement combined with the MALLS technique (cf. document L12).

(ii.9) An alternative method was to use a viscometer, such as an Ubbelohde viscometer (cf. L20).

(ii.10) Consequently, it was believed that the intrinsic viscosity was sufficiently disclosed in the patent.

(ii.11) Kd was a parameter which told the skilled person what type of chromatography column to use (cf. L19).

(ii.12) The Board had misunderstood the comments of the undersigned in his letter of 23 December 1999, at page 21, third paragraph.

(ii.13) As explained by L19 (paragraph 8) and L1 (page 150), the value of Kd was relatively insensitive to the amount of buffer used, provided that conventional quantities were utilised.

(ii.14) Further, there was no suggestion in the specification that any solvent other than water would be used when chromatographing pneumococcal polysaccharides.

(ii.15) The skilled person would again assume that measurements should be made at room temperature absent other instructions. In any event, no evidence of any appreciable change in Kd between 20 and 25°C had been submitted by the Opponent in these proceedings.

(ii.16) Choosing an appropriate flow rate for use in a particular column was part of the common general knowledge of the skilled person. No evidence had been submitted to the contrary.

(ii.17) Columns were designed for particular flow rates, and using columns within the manufacturer's specifications would enable appropriate values of Kd to be obtained.

(ii.18) The patent provided exemplary columns, which in any case were part of the common general knowledge, the skilled person would use a very conventional solvent (water), a conventional temperature (room temperature) and column-specific standard flow rates.

(ii.19) Concerning target end-point viscosities, it was noted that the Opposition Division had not found this term to be insufficiently disclosed.

(ii.20) The skilled person would conventionally measure target end-point viscosities in water.

(ii.21) Target end-point viscosities were given as ranges rather than precise values. Each range varied by more than 15%. It would not therefore, matter whether measurements were made at 20°C or 25°C since the end point viscosity range was wide enough to encompass this variation.

XI. With its letter dated 21 November 2006, the Appellant submitted the following document:

L20A: Second declaration of Dr Michael Gentzler.

XII. In its letter dated 28 November 2006 the Respondent argued essentially as follows:

(i) The new requests and the new declarations had been filed at a very late stage. Their filing amounted to an abuse of procedure. They should not be admitted.

(ii) Concerning sufficiency of disclosure:

(ii.1) The burden was now on the Appellant to prove that the decision of the opposition division was incorrect.

(ii.2) The measurement of K_d was sensitive to change of conditions, in particular buffer conditions, and the patent did not disclose the method for determining K_d in a manner which reliably retained the validity of this parameter for the solution to the technical problem.

(ii.3) Concerning intrinsic viscosity, the preferred method of measurement advocated by the application as

filed was given at the second paragraph on page 5 of the application as filed.

(ii.4) This was a method of measuring the reduced viscosity at a single unspecified concentration and equating this to be the intrinsic viscosity. This "preferred method" of assessing intrinsic viscosity was concentration dependent.

(ii.5) Reference was also made in that respect to document L12 (paragraph 14).

(ii.6) The patent did not disclose such concentration information in a manner which reliably retained the validity of the intrinsic viscosity parameter for the solution to the technical problem.

(ii.7) In respect of target end-point viscosity, evidence had been provided by the Respondent (paragraphs 16 and 17 of L9) that this measurement was significantly temperature dependent.

(ii.8) The patent in suit did not disclose such temperature information in a manner which reliably retained the validity of the end-point viscosity parameter for the solution to the technical problem.

(iii) A substantial procedural violation did not take place at first instance. The Patentee's behaviour and submissions up until 17 November 2006 were consistent with a party who was fully aware of the situation to the extent that no hint of a procedural violation was alluded to in the section of the appellant's statement of appeal concerning this point of appeal.

XIII. In its letter dated 30 November 2006, the Appellant argued essentially as follows:

(i) Paragraph III of the Annex to the Summons to Oral Proceedings contemplated that amendments could be made.

(ii) Documents L20 and L20A had been submitted in response to points raised by the Board.

XIV. Oral proceedings were held before the Board on 20 December 2006.

(a) At the oral proceedings, following preliminary observations from the Board as to whether or not the ground of opposition under Article 100(c) EPC had been introduced by the Opposition Division at the oral proceedings of 16 April 2003, and hence as to whether the refusal of the first auxiliary request by the Opposition Division would amount to a procedural violation or merely to an error in law, the Appellant indicated that it withdrew its request for reimbursement of the appeal fee.

(b) The Board having informed the Parties that the ground of opposition under Article 100(c) EPC did not form part of the proceedings, the Appellant submitted a new main request and a new auxiliary request each consisting of 1 claim which replaced the requests previously on file.

The Claim of the main request reads as follows:

"A pneumococcal polysaccharideimmunogenic protein conjugate produced by the process of:
(a) Culturing a pneumococcus and isolating crude pneumococcal polysaccharide or solubilizing pneumococcal polysaccharide powder;
(b) Purifying and partially-hydrolyzing the polysaccharide of step (a) to an endpoint predetermined to generate a polysaccharide amenable to conjugation having no more than a 30% reduction of the polysaccharide's type-specific antigenicity as compared with the crude polysaccharide of step (a); and
(c) Conjugating the product of step (b) with an immunogenic protein, wherein the pneumococcus cultured in step (a) is selected from one or more of the subtypes: 4, 6B, 9V, 14, 18C, 19F, and 23F, wherein the Pn-Ps retains its antigenic integrity as measured by Ouchterlony double immunodiffusion or rate nephelometry assay using an anti-Pn-Ps type-specific antibody, said Pn-Ps prior to conjugation being physically sheared in a Gaulin press at a pressure between about 13.8 MPa and 103 MPa (2000 and 15000 PSI) or hydrolyzed by heating at 100°C for 24 hours."

The Claim of the auxiliary request reads as follows:

"A pneumococcal polysaccharideimmunogenic protein conjugate produced by the process of:
(a) Culturing a pneumococcus and isolating crude pneumococcal polysaccharide or solubilizing pneumococcal polysaccharide powder;
(b) Purifying and partially-hydrolyzing the polysaccharide of step (a) to an endpoint predetermined to generate a polysaccharide amenable to conjugation having no more than a 30% reduction of the

polysaccharide's type-specific antigenicity as compared with the crude polysaccharide of step (a); and
(c) Conjugating the product of step (b) with an immunogenic protein, wherein the pneumococcus cultured in step (a) is selected from one or more of the subtypes: 4, 6B, 9V, 14, 18C and 19F, wherein the Pn-Ps retains its antigenic integrity as measured by Ouchterlony double immunodiffusion or rate nephelometry assay using an anti-Pn-Ps type-specific antibody, said Pn-Ps prior to conjugation being physically sheared in a Gaulin press at a pressure between about 13.8 MPa and 103 MPa (2000 and 15000 PSI) or hydrolyzed by heating at 100°C for 24 hours or by sonicating, to a K_d (peak) endpoint as follows for each listed Pn-Ps subtype:

Pn-Ps Subtype	Target Endpoint K_d (peak)
Pn4-Ps	0.65 ± 0.05
Pn6B-Ps	0.60 ± 0.05
Pn9V-Ps	0.65 ± 0.05
Pn14-Ps	0.60 ± 0.05
Pn18C-Ps	0.65 ± 0.05
Pn19F-Ps	0.65 ± 0.05

."

The discussion focussed on the admission of these requests into the proceedings and on their formal allowability under Article 123(2) and 123(3) EPC.

The arguments presented by the Parties in that respect may be summarized as follows:

(b.1) By the Appellant:

(b.1.1) In view of the decision announced by the Board in the parallel appeal case T 466/05 at the oral proceedings of 19 December 2006, concerning the lack of sufficiency in respect to the indication of the molecular weight of the pneumococcal polysaccharides, it had become necessary to reformulate the requests in order to avoid a rejection of the present appeal on the same grounds.

(b.1.2) These requests were based on granted Claim 6. Their subject-matter did not result in an increased complexity for the assessment of sufficiency of disclosure.

(b.1.3) The deletion of the reference to the end-target viscosity and to the end target K_d in the claim of the main request did not lead to an extension of scope since the obtaining of these properties was linked only to the use of the sonicating step. Reference was made in that respect to page 13, lines 13 to 15 and 20 to 23, and to Example 10 of the patent specification.

(b.1.4) The deletion in the claim of the auxiliary request of the mention of the subtype 23F did not infringe Article 123(2) EPC. Reference was made in that respect to page 13, line 36 of the patent specification.

(b.2) By the Respondent:

(b.2.1) These requests should not be admitted since they were very late filed.

(b.2.2) Reference was made to Article 10b(1) of the Rules of Procedure of the Boards of Appeal (RPBA) in that respect.

(b.2.3) While no objection under Article 123(2) EPC or Article 84 EPC was raised by the Respondent against the main request, it submitted that this request did not fulfil the requirements of Article 123(3) EPC. Contrary to the submissions made by the Appellant, it was considered that the expression "to a viscosity for….or K_d (peak) endpoint" in granted Claim 6 found its antecedent in the wording "said Pn-Ps prior to conjugation" in the same phrase of that claim, and hence equally applied to the physically shearing in a Gaulin press at a pressure between about 13.8 MPa and 103 MPa (2000 and 15000 PSI) and the hydrolysis by heating at 100°C for 24 hours.

(b.2.4) Concerning the first auxiliary request it was only submitted that the deletion of the subtype 23F led to an undisclosed selection contrary to Article 123(2) EPC.

(c) The Board informed the Parties that the main request was admitted into the proceedings and was regarded as meeting the requirements of Article 123(3) EPC, and that it had no objection of its own under Article 123(2) or Article 84 EPC concerning this request. The discussion then moved on the assessment of the sufficiency of disclosure of the subject-matter of that request. The arguments presented by the Parties in that respect may be summarized as follows:

(c.1) By the Respondent:

(c.1.1) The antigenicity index was determined in respect of a "crude" polysaccharide. Even if it would be considered that the crude polysaccharide would be obtained from the ATCC, document L6 showed that there were very important differences between lots of subtypes of polysaccharide in terms of molecular weight and hence in term of starting antigenicity.

(c.1.2) Furthermore, it was not clear which antibody should be used when carrying out the antigenicity test. The results depended on the type of antibody used. There was hence a need for a reference.

(c.1.3) Anti Pn-Ps antibodies were prepared using crude Pn-Ps polysaccharides. They differed from one preparation to the other. They were polyclonal antibodies and they would bind to different antigens present in the crude polysaccharide.

(c.1.4) It would not be possible to distinguish the relevant part of anti-pneumococcal type-specific antibody binding in the precipitate.

(c.1.5) The crude polysaccharide might contain up to 60% by weight of C-polysaccharide. It would not be possible to distinguish between the antigen-antibody complex precipitate resulting from this part of the crude polysaccharide and the one resulting from the specific Pn-Ps antigen-antibody complex.

(c.2) By the Appellant:

(c.2.1) The antigenicity test was well established since 1986.

(c.2.2) The antibodies selected for carrying the antigenicity test were well defined commercial products and were specific to the Ps-Pn antigen. It was also possible to use a monoclonal antibody.

(c.2.3) The presence of C-polysaccharide would hence not affect the outcome of the test. Furthermore the fact that the patent in suit mentioned a 20 fold reduction of the amount of C-polysaccharide did not imply that the crude polysaccharide might contain up to 60% C-polysaccharide.

(c.2.4) The test was not an absolute test but a relative test. There was hence no need for a reference.

(d) The Board, after deliberation, having informed the Parties that the main request was regarded as meeting the requirements of Article 83 EPC, and having expressed the view that no opinion on the novelty of the subject-matter of the claim of the main request had indeed been formulated by the Opposition Division, the Respondent indicated that it would not be opposed to a remittal of the case to the first instance.

XV. The Appellant requested that the decision under appeal be set aside and the case be remitted to the first instance for further prosecution on the basis of the main request, or in the alternative, on the basis of the auxiliary request, both filed at oral proceedings.

The Respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Procedural matters*

2.1 As can be seen from the Facts and Submissions the Board has been confronted with the following procedural issues:

(i) the questions of whether or not the ground of opposition under Article 100(c) EPC had been introduced into the proceedings by the Opposition Division and the procedural consequences of the introduction or of the non introduction of this ground into the proceedings, and

(ii) the question as to whether the requests submitted by the Appellant at the oral proceedings before the Board should be admitted into the proceedings.

2.2 Concerning point (i):

2.2.1 As indicated above in Section III, the first auxiliary request submitted by the Patent Proprietor at the oral proceedings before the Opposition Division has been refused because Claim 1 thereof did not meet the requirements of Article 123(2) EPC.

2.2.2 According to the decision of the Opposition Division, there was no basis in the application as originally filed for the feature in Claim 1 of that request that

the lower limit of the molecular weight Mw of the polysaccharide derived from Streptococcus pneumoniae 4 be 2 x 10^5.

2.2.3 In that respect, the Board notes that Claim 1 of the first auxiliary request was based on a combination of Claims 1, 2, 3 and 4 as granted, and that Claim 4 as granted already contained the objected feature.

2.2.4 This implies, in the Board's view, that the presence of this feature in Claim 1 of the first auxiliary request could only have been open to an objection under Article 123(2) EPC, provided the ground of opposition under Article 100(c) EPC would have been in the opposition proceedings.

2.2.5 In this connection, the Board, however, observes that, in the Notice of Opposition dated 19 May 1999 only the grounds of opposition under Article 100(a) and 100(b) EPC were mentioned.

2.2.6 While in its letter dated 14 February 2003, the Opponent had requested that "as a result of the claim **amendments** made by the Patentee as a main request in their submission of 29 December 1999 the claims are revoked under new grounds of Article 100(c)" (emphasis by the Board), the Board can only state that no objection under Article 100(c) EPC has been raised in substance by the Opponent against the claims as granted.

2.2.7 In view of the minutes of the oral proceedings before the Opposition Division and the decision of the Opposition Division, it is further not apparent as to

whether a discussion and a decision on the admission of this new ground of opposition had taken place.

2.2.8 In this connection, the Board also observes there would have been no need for the Opposition Division to introduce this new ground of opposition, in order, as requested by the Opponent, to check the allowability of amendments made in the course of the opposition proceedings by the Patent Proprietor under Article 123(2) EPC, since, as stated in the decision G 9/91 (OJ EPO 1993, 408; Reasons point 19) in case of amendments of the claims or other parts of a patent in the course of opposition or appeal proceedings, such amendments are to be fully examined as to their compatibility with the requirements of the EPC e.g. with regard to the provisions of Article 123(2) and (3) EPC.

2.2.9 The Board further observes that, in its decision (cf. page 4, Formal aspects, lines 6 to 9), the Opposition Division had decided to adopt any conclusion reached in the opposition proceedings concerning the parallel European patent application No. 92 300 654.8. This implies that the Opposition Division had also taken the view that the main request on which its decision was based met the requirements of Article 123(2) EPC (cf. minutes of the oral proceedings of 15 April 2003 in the case of the European patent application No. 92 300 654.8, page 2, lines 1 to 2), although Claim 4 of this request, which corresponded to Claim 4 as granted, already contained the feature which had led to the refusal of the first auxiliary request. This suggests, in the Board's view, that the ground of opposition under Article 100(c) EPC had not been

introduced into the opposition proceedings by the Opposition Division, otherwise the main request should also have been refused on the grounds of Article 123(2) EPC by the Opposition Division.

2.2.10 The Board also notes that the Appellant has submitted that there was no discussion concerning the admission of the ground of opposition under Article 100(c) EPC into the proceedings at the oral proceedings before the Opposition Division (cf. letter dated 17 November 2006, page 4, second paragraph) and that this had not been disputed by the Respondent.

2.2.11 Under these circumstances, it is hence more than likely, in the Board's view, that the ground of opposition under Article 100(c) EPC had not been introduced into the opposition proceedings by the Opposition Division, and that the Opposition Division had erroneously handled the combination of granted Claims 1, 2, 3 and 4 which resulted in Claim 1 of the first auxiliary request as representing an amendment open to objection under Article 123(2) EPC in accordance with Article 102(3) EPC. Thus, the Board comes to the conclusion that Article 100(c) EPC does not form part of the opposition/appeal proceedings.

2.2.12 Furthermore, it also follows from the above that the error in law which led to the refusal of the first auxiliary request has to be regarded, in the Board's view, as an error of judgement but not as a substantial procedural violation which might have justified setting aside the decision under appeal.

2.3 Concerning point (ii):

2.3.1 As indicated above in paragraph XIV, the Appellant has submitted at the beginning of the oral proceedings of 20 December 2006 a new main request, and a new auxiliary request.

2.3.2 In the Board's view, the question of the admissibility of the late filed requests should be considered in the context of the parallel appeal proceedings (i.e. T 466/05) concerning the European patent application No. 92 300 654.8.

2.3.3 At the end of the oral proceedings concerning that appeal case which took place on 19 December 2006, the Appellant (Patent Proprietor) was informed that the requests on file did not meet the requirements of Article 83 EPC, in particular in view of the reference in the claims of these requests to the molecular weight between 10^5 to 10^6 of the pneumococcal polysaccharides.

2.3.4 Since at least Claim 1 of all the requests submitted by the Appellant in the present case with its letter dated 17 November 2006 also contained a reference to the molecular weight of the pneumococcal polysaccharides, the filing of a request in which the claim is devoid of this feature is, in the Board's view, to be considered as a legitimate attempt to avoid a rejection of the present appeal for the reasons which led to the refusal of the appeal in the copending case.

2.3.5 Since the Claim of the main request is essentially based on granted Claim 6, the late filing of this request does not, in the Board's view, create any

complex situation for the Respondent and cannot hence be considered to result for it in any surprise or difficulty in properly addressing the points at issue, i.e. conformity of the claim with Article 123(3), 123(2) and 84 EPC, and sufficiency of disclosure.

2.3.6 Consequently, the Board, making use of its discretion under Article 10b RPBA, decides to admit the main request into the proceedings.

Main request

3. *Wording of the Claim*

3.1 The Claim of the main request differs from Claim 6 as granted in that the following passage "or by sonicating, to a viscosity for a 1 mg/ml solution in 0.9 M sodium chloride or K_d (peak) endpoint as follows for each listed Pn-Ps subtype:

Pn-Ps Subtype	Target Endpoint Viscosity (centistokes)	Target Endpoint K_d (peak)
Pn4-Ps	1.5 - 1.00	0.65 ± 0.05
Pn6B-Ps	1.3 - 1.00	0.60 ± 0.05
Pn9V-Ps	1.3 - 1.00	0.65 ± 0.05
Pn14-Ps	1.1 - 0.95	0.60 ± 0.05
Pn18C-Ps	1.5 - 1.00	0.65 ± 0.05
Pn19F-Ps	1.3 - 1.00	0.65 ± 0.05
Pn23F-Ps	1.5 - 1.00	0.54 ± 0.05;

optionally followed by chromatographic or alcohol fractionation to select material having a polydispersity below 1.4." has been deleted therefrom.

3.2 Consequently, it must be firstly examined as to whether the deletion of this passage gives rise or not to an extension of scope of protection over that conferred by granted Claim 6 (Article 123(3) EPC).

3.2.1 In that respect, it is clear that the question of extension of scope of protection boils down to the question as to whether the reference to a target endpoint viscosity or to a target endpoint K_d applies only to the sonicating step or equally also to the steps of physically shearing in a Gaulin press at a pressure between about 13.8 MPa and 103 MPa (2000 and 15000 PSI) and/or of hydrolyzing by heating at 100°C for 24 hours.

3.2.2 In this connection, while the description of the patent in suit clearly and unambiguously associates the number of cycles of sonic treatment to be carried out with the target endpoint viscosity or the target endpoint K_d to be reached (cf. patent in suit, page 13, lines, 14 to 15), the Board firstly observes that the hydrolyzing step is defined in the Claim of the main request as in granted Claim 6 by the temperature at which it is carried out (100°C) and by its duration (24 hours), so that the characteristics of the hydrolyzed polysaccharide in terms of reduction of antigenicity are evidently only the direct result of these fixed hydrolysis reaction parameters (temperature and duration). This implies that the reference to a target end point viscosity or to a target endpoint K_d made in granted Claim 6 cannot not apply to the hydrolyzing step.

3.2.3 Concerning the physical shearing in a Gaulin press, it is, in the Board's view, derivable from the patent in suit (cf page 13, lines 20 to 23; Example 10) that its conditions are predetermined in order to obtain a reduced antigenicity, and that there is no necessity to fix a target endpoint viscosity or a target endpoint Kd for the polysaccharides subjected to this physical shearing step. The reference to a target end point viscosity or to a target endpoint K_d made in granted Claim 6 cannot therefore be considered as applying to the physical shearing step.

3.2.4 Consequently, the reference to the obtaining of a specific target endpoint viscosity or a specific target endpoint K_d made in granted Claim 6 must be regarded as applying only to the sonicating step.

3.2.5 It thus follows that the deletion of the alternative relating to the sonicating treatment does not lead to an extension of scope of protection but to the contrary to a restriction of that scope of protection.

3.2.6 Consequently, the Claim of the main request meets the requirements of Article 123(3) EPC.

3.3 Since, as mentioned above in paragraphs 3.2.4 and 3.2.5, the Claim of the main request differs from granted Claim 6 only by the deletion of an alternative (sonicating step), it thus follows that its subject-matter has been merely restricted to the other remaining alternatives (i.e. physical shearing or hydrolyzing) already claimed in granted Claim 6.

3.4 This has for its consequence, that the Claim of the main request is not susceptible and therefore not open either to objection under Article 123(2) EPC since, as further indicated above, Article 100(c) EPC does not form part of the present opposition/appeal proceedings, or to objections under Article 84 EPC (cf. also decision T 301/87; OJ EPO 1990, 335).

4. *Sufficiency of disclosure*

4.1 The Claim of the main request is formulated as a product by process claim. Consequently, the reproduction of the claimed invention presupposes that the skilled person would be able to carry out the process mentioned in that claim for obtaining the claimed pneumococcal polysaccharideimmunogenic protein conjugate.

4.2 In that respect, it is evident that the key feature of the process is the obtaining of a polysaccharide, exhibiting, prior to conjugation, a reduction of up to 30% of antigenicity as compared with the crude polysaccharide of step (a) of the process.

4.3 This implies, in the Board's view, that the Claim of the main request as such does not define the antigenicity of the pneumococcal polysaccharide before conjugation in absolute terms but that it merely requires that during the preparation of the conjugate there must some retention of the antigenicity of the polysaccharide of step (a) of the process.

4.4 Consequently, the question of sufficiency boils down to the question as to whether the skilled person is

instructed by the patent in suit (i) as how to determine a **relative** reduction of antigenicity of the polysaccharide and (ii) as how to achieve such reduction.

4.5 Concerning point (i), there can be no doubt, in the Board's view that, using a method such as the rate nephelometry referred to in the patent in suit (cf. page 5, lines 33 to 43) the pneumococcal polysaccharide at the end of the step (a) can be tested for antigenicity using its specific antibody which reacts with it in order to establish a reference value i.e. antigenicity index of 1 and that at the end of the physical shearing step or of the hydrolyzing step, the antigenicity of the thus obtained pneumococcal polysaccharide could be tested using the same specific antibody as for the polysaccharide obtained at the end of step (a) and thus defining its relative antigenicity in respect of the polysaccharide of step (a).

4.6 In other words, the fact that different sources of antibody sera might be used (cf patent in suit page 6, lines 7 to 11) or that the starting polysaccharide might vary considerably from lot to lot as shown by document L6 cannot be relevant for challenging the sufficiency of disclosure of the subject-matter of the Claim of the main request because of the relative nature of the antigenicity relied on in the process for making the claimed conjugate, which evidently imposes that the **same** antibody should be used for testing both the polysaccharide obtained at the end of step (a) and the polysaccharide obtained after the physical shearing step or the hydrolyzing step.

4.7 Concerning point (ii), there can also be no doubt that the skilled person would be able to determine appropriate conditions of physical shearing in order to get the desired retention of antigenicity (cf. patent in suit page 13, lines 20 to 23) or to check whether the hydrolysis process is adapted to the specific pneumococcal polysaccharides of step (a) in order to obtain the desired retention of antigenicity.

4.8 Consequently, the Board comes to the conclusion that the patent in suit provides sufficient instructions in order to obtain a conjugate as defined in the Claim of the main request. The Board is hence satisfied that the main request meets the requirements of Article 83 EPC.

5. Under these circumstances, there is hence no need for the Board to decide on the admission of the auxiliary request of the Appellant into the proceedings or to deal with the conformity of this request with Articles 123(3), 123(2), 84 and 83 EPC.

6. *Remittal*

6.1 Whilst it would *prima facie* appear that the Opposition Division had expressed the view that the subject-matter of Claim 3 of the second auxiliary request which corresponded to Claim 6 as granted met the requirements of Article 54 EPC, the Board observes that in its decision (cf. page 25 thereof, lines 13 to 15) the Opposition Division had considered that Claim 3 referred "to the Pn-Ps of Claim 1", although Claim 3 was an independent claim and did not refer to the specific Pn-Ps defined in Claim 1 of the second auxiliary request.

6.2 It thus follows that the assessment of novelty of the subject-matter of Claim 3 of the second auxiliary request has been made on the basis of an alleged but unfounded dependency of that claim on Claim 1 of that request.

6.3 This implies, in the Board's view, that the Opposition Division has not reached a final determination on the issue of novelty of the "true" subject-matter of that Claim 3, i.e. of the subject matter of granted Claim 6, and by way of consequence, of the subject-matter of the Claim of the present main request.

6.4 Consequently, the Board, having taken into account the request of the Appellant for remittal and the fact that the Respondent had indicated at the oral proceedings before the Board that it had no objection against such remittal, in the exercise of its discretionary power pursuant to Article 111(1) EPC, finds it appropriate to remit the case to the first instance for further prosecution.

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 for further prosecution on the basis of the main request filed at oral proceedings.

The Registrar: The Chairman:

E. Görgmaier R. Young