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D E C I S I O N
of 31 January 1996

Case Number: T 0588/93 - 3.3.2

Application Number: 84113358.0

Publication Number: 0143369

IPC: B01J 20/32

Language of the proceedings: EN

Title of invention:
A porous adsorbent for adsorbing low density lipoproteins

Patentee:
Asahi Kasei Kogyo Kabushiki Kaisha

Opponent:
01: P. Braun Melsungen AG
02: Fresenius AG

Headword:
Porous Adsorbent/ASAHI KASEI KOGYO KABUSHIKI KAISHA

Relevant legal provisions:
EPC Art. 123(2)(3), 102(3), 84, 83, 56

Keyword:
"Inventive step of main request - yes - provision of an alternative material in a non-obvious way"

Decisions cited:
T 0292/85, T 0100/90

Catchword:
-

Case Number: T 0588/93 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 31 January 1996

Appellant: (Proprietor of the patent)	Asahi Kasei Kogyo Kabushiki Kaisha 2-6, Dojimahama 1-chome Kita-ku Osaka-shi Osaka 530 (JP)
Representative:	Strehl Schübel-Hopf Groening & Partner Maximilianstrasse 54 D-80538 München (DE)
Respondent(s): **(Opponent 01)**	P. Braun Melsungen AG Karl-Braun-Strasse 1, Postfach 1 20 D-34209 Melsungen (DE)
Representative:	Huber, Bernhard, Dipl.-Chem. Patentanwälte H. Weickmann, Dr. K. Fincke F. A. Weickmann, B. Huber Dr. H. Liska, Dr. J. Prechtel, Dr. B. Böhm Postfach 86 08 20 D-81635 München (DE)
Opponent 02:	Fresenius AG D-61343 Bad Homburg v.d. Höhe (DE)
Representative:	Dr. Fuchs, Dr. Luderschmidt Dr. Mehler, Dipl.-Ing. Weiss Patentanwälte Postfach 46 60 D-65036 Wiesbaden (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 26 April 1993 revoking European patent No. 0 143 369 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: F. Antony
Members: U. Oswald
R. E. Teschemacher

Summary of Facts and Submissions

I. European patent No. 0 143 369 relating to a porous adsorbent for adsorbing low density lipoproteins was granted on 18 October 1989, with eleven claims, in response to European patent application No. 84 113 358.0 filed on 6 November 1984 and claiming priorities from Japanese applications JP 220532/83 filed on 25 November 1983; JP 5678/84 filed on 18 January 1984; JP 96375/84 filed on 16 May 1984; JP 97501/84 filed on 17 May 1984 and JP 98597/84 filed on 18 May 1984.

II. Two oppositions were filed by B. Braun Melsungen AG (Opponent 01) on 22 June 1990 and by Fresenius AG (Opponent 02) on 14 July 1990.

Of the numerous documents cited during the Opposition, only the following remain relevant for the present decision:

(A) DE-A-3 115 608

(B) DE-A-3 225 603.

III. By a decision of the Opposition Division dated 26 April 1993 the patent was revoked pursuant to Article 102(1) EPC. The decision under appeal took the view that the subject matter of the patent in suit, based on Claim 1 as amended on 14 May 1991, was sufficiently disclosed and novel, but lacked an inventive step within the meaning of Article 56 EPC over the closest prior art reference (B).

Said amended Claim 1 reads as follows:

"1. A porous adsorbent for adsorbing thereonto a low density lipoprotein which comprises a surface and, linked with the surface, at least one member selected from a silanol group and a synthetic polyanion member having a molecular weight of 600 or more, and which absorbent has pores, whereby (1) the pore diameters of pores occupying 70% or more of pore volume based on the total pore volume of the adsorbent are distributed in the range of 20 nm to 1,250 nm, and (2) the pore volume of pores having a diameter in the range of 0.8 D to 1.2 D wherein D represents the pore diameter of any one of the pores having pore diameters in the range of 20 nm to 1,250 nm is 75% or less based on the total pore volume of the adsorbent."

More particularly, the decision under appeal held that the problem underlying the patent in suit was to search for a more effective selective separation of low density lipoproteins (LDL). The proposed solution, being in essence a comparatively broad distribution of pore diameters, with 75 % or less in a given range, was not conclusively shown to be critical for a more selective separation of LDL. Moreover, the adsorbent of Example 4 of reference (B) having a sharp diameter distribution showed a very effective LDL removal.

IV. On 1 July 1993, the Appellant (Patentee) lodged an appeal against the decision of the Opposition Division, followed by a Statement of Grounds on 6 September 1993. Oral proceedings took place on 31 January 1996. In accordance with his letter dated 10 January 1996, one of the Respondents (Opponent 01) did not attend the oral proceedings, nor had he filed any written arguments at the appeal stage.

The arguments of the Appellant, both in writing and at the oral proceedings may be summarised as follows:

The problem underlying the patent in suit was to provide an adsorbent which effectively allows the selective adsorption of LDL from blood plasma while the desired proteins essentially remain in the plasma. The closest prior art according to reference (B) neither mentioned any such selectivity, nor could the adsorbent disclosed therein actually achieve such a selective removal. Moreover, this prior art taught away from the claimed subject matter by expressly emphasising the importance of a comparatively sharp pore size distribution. The adsorbent of the invention showed an extremely broad pore size distribution and thus, the adsorption of LDL was based on a totally different technical concept. Accordingly, it was inappropriate to draw any conclusions from the functional relationship of the LDL remaining rate and total pore volume by mixing up data derived from adsorbents having sharp and adsorbents having broad pore size distribution. The Opponents had not filed any experimental evidence for their assertion that the adsorption selectivity as required by the patent in suit was exclusively based on the total pore volume of the adsorbent.

V. The Respondent (Opponent 02) contested these arguments and stated that it was necessary to take into account the common general knowledge about molecular sieve technology, viz. that both, the pore size and the specific type of ligand on the inner and outer surface of the porous adsorbent would influence the adsorption selectivity. Accordingly, adsorbents could be functionally designed in view of each of those parameters taken separately. It was therefore also possible to use, in a separation process for a mixture of various lipoproteins, ligands having for example high affinity to LDL and very weak affinity to the high density lipoproteins (HDL component). The prior art according to references (A) and (B) described both, the ligand effect and the pore size effect, and contained information about the adjustment of pore size values suitable in a selective adsorption process for different types of proteins. It was furthermore common general knowledge that, on the one hand the adsorption capacity depended on the specific surface area and, on the other hand the specific surface was correlated with the pore volume. This relationship was supported by "Anlage 1" attached to his letter dated 24 January 1994 showing, by way of a graph, the experimental data available from the patent in suit and from comparative experiments, plotting the remaining rate LDL [%] versus the total pore volume [cm^3/g]. Said graph illustrated clearly that the low remaining rates of LDL achieved by the adsorbent of the patent in suit could only be interpreted as resulting from increasing pore volume. Accordingly said remaining rates were not correlated with the pore size distribution as presently claimed.

Furthermore, it was necessary to take into account that the patent in suit and reference (B) were using the same porous glass as raw material for the adsorbent carrier and the worked examples of (B) showed pore volume values of the finished adsorbent which were very close to those of the patent in suit; hence reference (B) obviously also comprised an alkali treatment of the porous glass as described in the patent in suit for achieving a pore size expansion leading to adjustment of the pore diameter distribution of the adsorbent. The said pore expansion, however, could not form the basis for an invention since the patent in suit did not disclose individual values of average pore diameters achieved by said alkali treatment. Apart from the fact that the lack of such disclosure could form the basis for an insufficiency objection, a pore size expansion greater than an average value of about 80 nm would in any case mean that the specific surface of the adsorbent had to be regarded as the only relevant parameter for the adsorption characteristic. In the light of all of these facts it was not possible for a person skilled in the art to get a clear understanding in which way the combination of parameters presently claimed contributed to the desired adsorption effect.

VI. The Appellant requested that the decision under appeal be set aside and that the patent be maintained with the set of claims submitted with the letter of 14 May 1991, with the correction in line 3 of Claim 1 according to which "absorbent" is replaced by "adsorbent", and the description of the patent as granted with the amendments filed with the letter of 14 May 1991, with the further amendment that on page 5, line 31 the word "generally" is deleted - main request,

or alternatively

on the basis of the set of claims submitted with the letter of 14 March 1995, with the same correction in Claim 1 as for the main request and a description yet to be adapted - auxiliary request.

The Respondent (Opponent 02) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. Claim 1 of the main request is based on Claim 1 originally filed and Claim 1 as granted and finds further support on page 17, lines 19 to 23 of the original description (page 5, lines 30 to 32 of the patent specification as granted). Claims 2 to 11 correspond to claims 2 to 11 as granted and originally filed. The claims are of narrower scope than the granted claims. The requirements of Article 123(2) and (3) EPC are accordingly satisfied.

   The description adapted to the amendments of Claim 1 of the main request also fulfils the requirements of Article 123(2) EPC.

3. In order to establish insufficiency of disclosure under Article 83 EPC, in the present case the burden of proof is on the Respondent. The mere statement that the description of the patent in suit does not contain values of the average pore diameter of the finished adsorbent is in the Board's opinion inadequate to discharge that burden. The Respondent has not filed any evidence that a person skilled in the art would be unable to carry out the invention as set out in the worked examples of the patent in suit or that it was impossible to obtain the values of pore volume according to these examples and defined in Claim 1. On the contrary, in his argumentation based on the graph according to "Anlage 1" attached to his letter dated 24 January 1994, the Respondent referred to the experimental results in the worked examples of the patent in suit. It is established case law of the Boards of Appeal that an invention is sufficiently disclosed

for the purpose of Articles 83 and 100(b) EPC if at least one way is clearly indicated, enabling the person skilled in the art to carry out the invention unless there is no technical concept fit for generalisation covering the ambit of the claim (see e.g. Decisions T 292/85, OJ EPO 1989, 275, T 435/91, OJ EPO 1995, 188).

Furthermore, Article 102(3) EPC provides no basis for objections under Article 84 EPC unless such objections would arise out of amendments after grant. In the present case the Board cannot see how a limitation merely lowering the value of a specific parameter from 80% to 75% of a specific parameter could introduce any ambiguity.

4. None of the documents cited during the proceedings discloses a porous adsorbent having all the features set out in Claim 1 of the main request. Since novelty is no longer in dispute, it is not necessary further to investigate this matter.

5. Document (B) was accepted by the Opposition Division and by each of the parties as representing the closest state of the art. The Board sees no reason to deviate from this point of view.

5.1 This prior art relates to substantially spherical, porous granules, preferably glass granules, to be used in a blood purification device as an adsorbent for substances such as low-density lipoprotein (LDL) beside other proteins. These granules were found to overcome the disadvantage of previously known adsorbents made of porous material, in particular of glass, of being in a crushed form with each granule having sharp edges, so that, when used in direct blood treatment, that material will reduce the leukocyte or platelet count. The spherical granules of (B) have at least 0.1 μ mole/m^2 of silanol groups on the apparent surface and on the surface within the micropores. Their pore volume is within the range of 0.3 cm^3/g to 2.0 cm^3/g, with a pore diameter of 20 Å to 3000 Å, whereby the ratio of the volume occupied by pores with diameters within the range 0.8 D to 1.2 D to the entire pore volume is at least 80 %, the symbol D standing for the mean pore diameter. When the granules have such a comparatively sharp pore diameter distribution, the use of porous granules having an appropriate pore diameter depending upon the molecular weight of the protein to be adsorbed can result in selective adsorption and removal of the target proteins. In this context it is expressly stated that the pore diameter distribution should be uniform because a broad pore diameter distribution would result in a reduced selectivity of protein adsorption as a function of the protein size. Furthermore, reference is made to the close relationship between the mean (average) pore diameter and the protein species to be adsorbed. It is then exemplified in the form of a listing how the adsorption of various protein species having different molecular weight may be achieved using mean pore diameters within defined ranges. Thus, e.g. for albumin with a molecular weight of 20000 to 200000 the use of porous granules having a mean pore diameter within the range of 150 Å to 1000 Å is suggested, for LDL having a molecular weight of several millions granules with a mean pore diameter from 900 Å to 1600 Å, and for fibrinogen having a molecular weight of 200 000 to 1 000 000 granules with a mean pore diameter of 1000 Å to 2500 Å (see page 6, lines 15 to 33; page 7, lines 1 to 5 and lines 29 to 33; page 8, lines 6 to 11; page 10, lines 7 to 10; page 11, line 11 up to page 12, line 6; page 12, line 8 up to page 13, line 25).

For better compatibility with the blood the granules may be coated with a hydrophilic polymer e.g. acrylic-acid-ester based polymers (see page 13, lines 28 to 30).

Example 4 on pages 21/22 of document (B) illustrates the removal from rabbit blood of cholesterol, which was said to be present in the LDL-bound form. The adsorption column used was packed with spherical porous glass granules having a mean pore diameter D of 1020 Å, a silanol group concentration of 0.47 μ mole/m^2, a volume ratio of 0.8 D to 1.2 D pores of 86%, a pore volume of 0.63 cm^3/g and a mean granule diameter of 1 mm. The percent cholesterol removal (or percent LDL removal) is indicated as 80%.

5.2 In the light of the afore-said prior art, the technical problem underlying the patent in suit can be seen in providing a further porous material suitable for selectively adsorbing LDL.

This problem is to be solved by the porous adsorbent according to Claim 1 of the main request (see paragraph III above). The experimental evidence in the description of the patent in suit illustrates remaining rates of LDL in plasma after adsorption treatment well below 50% and remaining rates for high density lipoproteins (HDL-C) as well as albumin and fibrinogen very close to 100%. As already set out under paragraph 3 above, the Respondent has not filed any evidence to the contrary. Accordingly, the Board is satisfied that the problem has indeed been solved.

6. It remains to be established whether the proposed solution involves an inventive step.

6.1 The Respondent is right in arguing that reference (B) clearly comprises the teaching that porous glass granules having a pore diameter adapted to the molecular weight of the protein to be adsorbed allow a selective adsorption and removal of the target proteins, and thus the closest prior art has to be discussed in the light of the same problem underlying the patent in suit. For LDL, having a molecular weight of several millions, the use of porous granules having a mean pore diameter within the range of 900 Å to 1600 Å is expressly mentioned in (B);see point 5.1 above.

In accordance with the established case law of the Boards of Appeal, however, when deciding on the question of inventive step in the present case, there is no need to show an improvement of the claimed adsorbent, whether substantial or gradual, over those adsorbents described in the prior art (see e.g. T 100/90 Technical Board of Appeal 3.2.3 dated 2 April 1991; EPOR 91, 553). In other words, a previous solution of a given technical problem does not preclude any subsequent attempt to solve the same problem in a further non-obvious way. In the present case, neither the general explanations according to the description, nor the specific results according to the worked examples of reference (B) contain the slightest hint to deviate from its teaching that a **sharp pore diameter distribution is essential for achieving a certain selectivity of the adsorption process**. This is particularly underlined by Example 4 illustrating that an LDL removal of 80% may be achieved by glass granules having a mean pore diameter D of 1020 Å and a volume ratio of 0.8 D to 1.2 D pores of 86%. While arguing that reference (B) and in particular said Example 4 would implicitly comprise the teaching to carry out a pore size expansion of the "raw" glass granules used, the Respondent has not contested the pore size distribution defined in that example. Taking into account the proposed decreased selectivity in protein adsorption when adjusting a broad pore size distribution according to reference (B), the Board sees no reason why the person skilled in the art, even taking into account the theoretical background of molecular sieves or the functional relationship between remaining rate of LDL and total pore volume, would get an incentive to modify the raw glass material for the carrier of the adsorbent in a sense **opposite** to the one recommended.

Even if one followed the Respondent's argument that the relative broadness of the pore size distribution as such would not be directly correlated with the selectivity of the adsorbent for proteins, Claim 1 according to the main request would in the light of the disclosure of reference (B) still provide a non-obvious alternative. As the selectivity of the material as such is undisputed, it is sufficient that the **essential features characterising the adsorbent material** could **not** be derived in an **obvious** manner from the prior art.

For the same reasons, the Respondent's arguments relating to the obviousness of the adsorbent function of the porous material are not convincing.

6.2 Since the porous adsorbent material according to reference (A), which also has a sharp pore size distribution essentially differs from that described in reference (B) only in that a non-spherical porous glass is used as carrier material, this prior art does not comprise any additional teaching more relevant than that discussed above.

6.3 The other prior art cited during the previous proceedings is also deemed to be of less relevance than reference (B) discussed above.

6.4 It is accordingly the Board's view that the subject matter of Claim 1 of the main request would not have been obvious from either citation taken singly or in combination. Thus, the required inventive step is not lacking and Claim 1 of the main request, together with dependent Claims 2 to 11 satisfy the requirements of Article 56 EPC.

7. Since the Board have found the Respondent's main request to be allowable, it is not necessary to consider the auxiliary request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent in the following version:

   Description: as granted with the amendments filed with the letter of 14 May 1991 on pages 2 and 5 of the patent specification, with the further amendment that on page 5, line 31 the word "generally" is deleted,

   Claims: Nos. 1 to 11 submitted with the letter of 14 May 1991, with the correction that in line 3 of Claim 1 the word "absorbent" is replaced by "adsorbent".

The Registrar: The Chairman:

P. Martorana F. Antony