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**Datasheet for the decision
of 27 June 2006**

Case Number: T 0138/02 - 3.3.05

Application Number: 96101098.0

Publication Number: 0723794

IPC: B01D 15/08

Language of the proceedings: EN

Title of invention:

Adsorbent for removing interleukins and tumor necrosis factor,
and process for removing the same

Applicant:

KANEGAFUCHI KAGAKU KOGYO KABUSHIKI KAISHA

Opponent:

-

Headword:

-

Relevant legal provisions:

EPC Art. 52(4), 54(1), (2), (5)

Keyword:

"Second medical use; novelty (no)"

Decisions cited:

G 0005/83, G 0001/83, G 0006/83, T 0227/91

Catchword:

-



Case Number: T 0138/02 - 3.3.05

D E C I S I O N
of the Technical Board of Appeal 3.3.05
of 27 June 2006

Appellant: KANEGAFUCHI KAGAKU KOGYO KABUSHIKI KAISHA
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 10 August 2001
refusing European application No. 96101098.0
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: M. Eberhard
Members: H. Engl
J. Willems

Summary of Facts and Submissions

- I. This appeal lies against the decision of the examining division posted on 10 August 2001 to refuse European patent application no. 96 101 098.0.
- II. The examining division held that claim 1 of all requests, then on file, although novel, lacked inventive step having regard to document D1: EP A 247 592. The requirements of clarity and sufficiency of disclosure were not met since the subject matter of the claims was not limited to a particular method of determining log P and to well-defined substances for which the value log P applies. The description was not enabling for the entire broad scope claimed.
- III. With the grounds of appeal the appellant filed new sets of claims as a main and three auxiliary requests.
- IV. The Board issued a first communication raising objections under Articles 123(2) and 84 EPC, having regard to the missing or incomplete definition of the f factor and undisclosed combinations of tumor necrosis factor (TNF) with certain illnesses recited in the claims. Moreover, use claim 1 of the main and auxiliary requests was considered to lack novelty over D1. The Board also provisionally commented on the potential allowability of Swiss type claims for the use of a material comprising a carrier and an immobilized compound for the manufacture of an adsorbent for a further therapeutic application. It pointed to certain significant differences between a classic medicament

and the adsorbent which is used in accordance with the application.

- V. With letter of 28 May 2006, the appellant submitted new claims as a main and three auxiliary requests.

Claim 1 of the main request reads as follows:

"1. Use of a material comprising a porous water-insoluble carrier and a compound covalently immobilized onto said carrier, wherein the compound to be immobilized onto said carrier satisfies a value $\log P$ of at least 2.50, in which P is the distribution coefficient in an octanol - water system, and the total of hydrophobic fragmental constants f of fragments of said compound covalently immobilized into said carrier is not less than 2.50, in which the hydrophobic fragmental constant f shows the hydrophobicity of various fragments which are determined by statistical management of many found values of $\log P$, for the manufacture of an adsorbent for the treatment of a disease selected from the group consisting of rheumatoid arthritis, systemic inflammatory response syndrome, sepsis, systemic lupus erythematosus, Lyme disease, osteoporosis, Kawasaki disease, gouty arthritis, endometritis, premature labor, Castleman's disease, chronic disease with proliferation, contact dermatitis, idiopathic fibroid lung, adult respiratory distress syndrome, inflammatory bowel disease, immune angiitis, glomerular nephritis, urinary tract infection, cardiac infarction, asthma, respiratory tract infection, perinatal infectious

disease and rejection in organ transplantation, by removing at least one cytokine selected from the group consisting of interleukin-1, interleukin-2, interleukin-6 and interleukin-8 from body fluid, wherein the distribution coefficient P is determined by dissolving the compound in octanol (or water), adding an equal volume of water (or octanol) thereto, shaking for 30 minutes, centrifuging for from 1 to 2 hours at 2000 rpm and measuring the concentrations of the compound in the octanol and water layers, and said carrier has at most 60 degrees contact angle with water."

Claims 1 and 2 of the first auxiliary request read as follows:

- "1. Use of a material comprising a porous water-insoluble carrier and a compound, wherein said material is obtainable by covalently immobilizing said compound onto said carrier, and wherein said compound immobilized onto said carrier is at least one member selected from the group consisting of n-heptylamine, n-octylamine, decylamine, dodecylamine, hexadecylamine, octadecylamine, 2-aminooctene, naphthylamine, phenyl-n-propylamine, diphenylmethanamine, n-heptyl alcohol, n-octyl alcohol, dodecyl alcohol, hexadecyl alcohol, 1-octene-3-ol, naphthol, diphenylmethanol, 4-phenyl-2-butanol, glycidyl ethers derived from the foregoing alcohols, n-octanoic acid, nonanoic acid, 2-nonenoic acid, decanoic acid, dodecanoic acid, stearic acid, arachidonic acid, oleic acid, diphenylacetic acid, phenylpropionic acid, halides, esters and amides of the foregoing acids, octyl

chloride, octyl bromide, decyl chloride, dodecyl bromide, octanethiol, dodecanethiol, n-octyltrichlorosilane, octadecyltrichlorosilane, n-octylaldehyde, n-caprinaldehyde and dodecylaldehyde, and wherein said carrier has at most 60 degrees of contact angle with water for the manufacture of an adsorbent for removing at least one cytokine selected from the group consisting of interleukin-1, interleukin-2, interleukin-6 and interleukin-8 and tumor necrosis factor from body fluid in an extracorporeal circulation treatment."

- "2. Use according to claim 1 of a material for the manufacture of an adsorbent for the application to a body fluid in an extracorporeal circulation treatment of a patient suffering from a disease selected from rheumatoid arthritis, systemic inflammatory response syndrome, sepsis, systemic lupus erythematosus, Lyme disease, osteoporosis, Kawasaki disease, gouty arthritis, endometritis, premature labor, Castleman's disease, chronic disease with proliferation, contact dermatitis, idiopathic fibroid lung, adult respiratory distress syndrome, inflammatory bowel disease, immune angiitis, glomerular nephritis, urinary tract infection, cardiac infarction, asthma, respiratory tract infection, perinatal infectuous disease and rejection in organ transplantation."

Independent Claim 2 of the second auxiliary request reads as follows:

- "2. Use of a material comprising a porous water-insoluble carrier and a compound, wherein said compound is covalently immobilized onto said carrier, said compound to be immobilized satisfies a value $\log P$ of at least 2.50, in which P is a distribution coefficient in an octanol - water system, and the total of hydrophobic fragmental constants f of fragments of said compound covalently immobilized onto said carrier is not less than 2.50, in which the hydrophobic fragmental constant f shows the hydrophobicity of various fragments which are determined by statistical management of many found values of $\log P$, and wherein said compound immobilized onto said carrier is at least one member selected from the group consisting of n-heptylamine, n-octylamine, decylamine, dodecylamine, hexadecylamine, octadecylamine, 2-aminooctene, naphthylamine, phenyl-n-propylamine, diphenylmethanamine, n-heptyl alcohol, n-octyl alcohol, dodecyl alcohol, hexadecyl alcohol, 1-octene-3-ol, naphthol, diphenylmethanol, 4-phenyl-2-butanol, glycidyl ethers derived from the foregoing alcohols, n-octanoic acid, nonanoic acid, 2-nonenoic acid, decanoic acid, dodecanoic acid, stearic acid, arachidonic acid, oleic acid, diphenylacetic acid, phenylpropionic acid, halides, esters and amides of the foregoing acids, octyl chloride, octyl bromide, decyl chloride, dodecyl bromide, octanethiol, dodecanethiol, n-octyltrichlorosilane, octadecyltrichlorosilane,

n-octylaldehyde, n-caprinaldehyde and dodecylaldehyde, for the manufacture of an adsorbent for the application to a body fluid of a patient suffering from a disease to remove from said body fluid at least one cytokine selected from the group consisting of interleukin-1, interleukin-2, interleukin-6 and interleukin-8 and tumor necrosis factor which are produced excessively in said body fluid, said disease being selected from rheumatoid arthritis, systemic inflammatory response syndrome, sepsis, systemic lupus erythematosus, Lyme disease, osteoporosis, Kawasaki disease, gouty arthritis, endometritis, premature labor, Castleman's disease, chronic disease with proliferation, contact dermatitis, idiopathic fibroid lung, adult respiratory distress syndrome, inflammatory bowel disease, immune angiitis, glomerular nephritis, urinary tract infection, cardiac infarction, asthma, respiratory tract infection, perinatal infectious disease and rejection in organ transplantation, and said carrier has at most 60 degrees of contact angle with water."

Claims 1 and 2 of the third auxiliary request read as follows:

- "1. Use of a material comprising a porous water-insoluble carrier and a compound, wherein said material is obtainable by covalently immobilizing said compound onto said carrier, and wherein said compound immobilized onto said carrier is at least one member selected from the group consisting of n-heptylamine, n-octylamine, decylamine,

dodecylamine, hexadecylamine, octadecylamine, 2-aminooctene, naphthylamine, phenyl-n-propylamine, and diphenylmethyleamine, and wherein said carrier has at most 60 degrees of contact angle with water, for the manufacture of an adsorbent for removing at least one cytokine selected from the group consisting of interleukin-1, interleukin-2, interleukin-6, interleukin-8 and tumor necrosis factor from body fluid in an extracorporeal circulation treatment."

- "2. Use according to claim 1 of a material for the manufacture of an adsorbent for the application to a body fluid in an extracorporeal circulation treatment for removing at least one cytokine selected from the group consisting of interleukin-1, interleukin-2, interleukin-6 and interleukin-8 from a patient suffering from a disease selected from rheumatoid arthritis, systemic inflammatory response syndrome, sepsis, systemic lupus erythematosus, Lyme disease, osteoporosis, Kawasaki disease, gouty arthritis, endometritis, premature labor, Castleman's disease, chronic disease with proliferation, contact dermatitis, idiopathic fibroid lung, adult respiratory distress syndrome, inflammatory bowel disease, immune angiitis, glomerular nephritis, urinary tract infection, cardiac infarction, asthma, respiratory tract infection, perinatal infectuous disease and rejection in organ transplantation."

VI. Oral proceedings were held on 27 June 2006 during which the appellant filed an additional set of claims as fourth auxiliary request.

Claim 1 of said fourth auxiliary request differs from claim 1 of the main request in that

"medicament" is inserted after the first occurrence of the word "adsorbent"; and
"by extracorporeal adsorptive removal of" replaces the expression "by removing".

VII. The appellant's essential arguments may be summarized as follows:

The claims related to the use of a certain material for the manufacture of an adsorbent which is capable of removing from body fluid any of a list of cytokines with the intention of thereby treating any of a list of diseases. Consequently, the requests would contain claims drafted as second medical use claims. In the appellant's view this format should be available not only for classic medicaments, as envisaged in G 5/83, but also for the presently disclosed adsorbents. There existed several categories of therapeutic tools, some of which were not taken up by the body and consumed during their use, but nevertheless would act on a body fluid in a defined manner and thus treat a specific disease.

The presently defined adsorbent may be considered as a further type of medicament, which is neither swallowed nor taken up by the body but which nevertheless would

change the composition of a body fluid and lead to the treatment of a specific disease.

The appellant admitted that there were differences between the adsorbent of the claimed invention and a classical medicament, the latter usually being swallowed, resorbed, modified and excreted. However, the adsorbent would also be provided with the aim of treating a disease of a patient, as defined in the claims. It was insignificant that the adsorbent would not be consumed during application. However, the material was changed because the interleukins and/or TNF bind to the adsorbent. The adsorbent could be likened to certain anion exchange materials which are swallowed, bind lipids, e.g. cholesterol, during their passage through the digestive apparatus and are excreted loaded with the lipid. While in theory it would be possible to regenerate the adsorbent, it would be highly improbable in reality to re-use a material which has already been in contact with a patient's body fluid. Therefore, for all practical purposes the adsorbent is consumed during its use. Following the definition in T 227/91 (Reasons, point 5.2), its use should be considered not to be a surgical one, but a therapeutic use. The appellant pointed out that although the adsorbent was not brought **into** the body, the final object of bringing the **patient's body into contact** with the adsorbent was the same.

In the appellant's view, the definition of a medicament should be that of a substance which is applied to a patient in order to treat a disease. The adsorbent of the claimed invention would satisfy this definition. The format of claims reserved for medicaments should

therefore also be available for the presently claimed invention.

The appellant argued that, due to the different change in blood composition and the different diseases to be treated, the claims were distinguished over D1.

The appellant also put forward arguments in support of the inventive step of the claimed subject matter.

VIII. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the set of claims of any of the main request or auxiliary requests 1 - 3, all filed with letter of 28 May 2006 or auxiliary request 4 filed during oral proceedings.

Reasons for the Decision

1. *Prior art*

Document D1: EP-A-0 247 592 describes the manufacture of an adsorbent from a porous inorganic or organic water - insoluble carrier and a compound immobilized onto it (see page 2, lines 43 - 46; page 3, lines 30 - 53; page 4, lines 9 - 30; page 5, lines 19 - 24; examples). In accordance with example 3, a preferred adsorbent consists of an n-octylamine immobilized porous cellulose hard gel (Cellulofine GC-700m by Chisso Corporation). This adsorbent is prepared in the same manner as the adsorbent of example 1 of the instant application. It is evident that the adsorbent disclosed in example 3 of D1 satisfies the conditions

recited in the present claims having regard to the log P and f factors and the contact angle, since the same compound is immobilized on the same carrier, using the same preparation method.

For the treatment of a body fluid of a patient, e.g. whole blood or plasma, the adsorbent of D1 can be used in two ways: The adsorbent is placed in a bag and mixed with the patient's blood to remove the desired proteins, followed by removing the adsorbent by filtering. The blood treated in this way is then returned to the patient (page 5, lines 25 - 31). In another method, a column packed with the adsorbent is connected to an extracorporeal circulation circuit and a patient's body fluid, which may be either whole blood or plasma, is passed through it (page 5, lines 32 - 35).

The prior art adsorbent is described as being suitable for adsorption of the proteins β_2 -micro-globulin and immunoglobulin L-chain (Bence - Jones protein) only, removal of which from a patient's body fluid should provide a treatment for the diseases primary amyloidosis, multiple myeloma, macroglobulinemia and malignant lymphoma (page 2, lines 22 - 39).

In contrast, the present application aims at removing the cytokines interleukin-1 (IL-1), IL-2, IL-6 and IL-8, and TNF (tumor necrosis factor), the former for the treatment of rheumatoid arthritis, systemic inflammatory response syndrome, sepsis, systemic lupus erythematosus, Lyme disease, osteoporosis, Kawasaki disease, gouty arthritis, endometritis, premature labor, Castleman's disease, chronic disease with proliferation, contact dermatitis, idiopathic fibroid

lung, adult respiratory distress syndrome, inflammatory bowel disease, immune angiitis, glomerular nephritis, urinary tract infection, cardiac infarction, asthma, respiratory tract infection, perinatal infectuous disease and rejection in organ transplantation; the latter (TNF) for the treatment of rheumatoid arthritis, arteriosclerosis and dialytic complications including dialytic related amyloidosis.

2. *Second medical use*

- 2.1 Article 54(5) EPC stipulates that the provisions of Article 54(1) to (4) EPC shall not exclude the patentability of any substance or composition, comprised in the state of the art, for use in a method referred to in Article 52(4) EPC, provided that its use for any method referred to in that paragraph is not comprised in the state of the art. Thus, a purpose - limited product protection can be obtained for a "first medical indication" of a known substance or composition, without having to restrict the claims to the substance or composition when in a form technically adapted to a specified therapeutic purpose (see G 5/83, Reasons, point 15). However, as pointed out above, such a first medical indication of the adsorbent used in the present application is already known from D1.

The question therefore arises whether the different medical indications (the differences in the intended use of the adsorbent, characterized by the different proteins to be removed) can confer novelty to the present claims in which further medical indications are stated.

2.2 No European patent may be granted with claims directed to a **method** for the treatment of the human or animal body by therapy, since pursuant to Article 52(4) EPC such a method shall not be regarded as an invention which is susceptible of industrial application within the meaning of Article 52(1) EPC. Furthermore, no patent may be granted with claims directed to the **use** of a substance or composition for the treatment of the human or animal body by therapy, since it was held in G 5/83 (OJ EPO 1985, 64) (Headnote I; Order 1; Reasons, point 13) that a claim directed to the said use "is in no way different in essential content from a claim directed to a "method of treatment of the human or animal body by therapy with the substance of composition".

2.3 However, G 5/83 (Headnote II; Order 2) also ruled that "a European patent may be granted with claims directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application". These claims to a second (or further) medical application ("Swiss type" claims) were approved for the first time by decisions G 1/83, G 5/83 and G 6/83 (OJ EPO 1985, 60, 64, 67). The essential contents of the said decisions are similar and in the following, reference will be made with respect to G 5/83. In accordance with the principles elaborated in these decisions a specific claim format was allowed for a second (further) medical indication of a substance already known as a medicament; namely claims directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application (G 5/83, Reasons, point 23 and Order 2).

2.4 In the case under consideration here, the appellant's main argument was that the claimed new therapeutic application of the adsorbent consisting in removing at least one cytokine selected from the group consisting of interleukin-1, interleukin-2, interleukin-6 and interleukin-8 and tumor necrosis factor from a patient's body fluid, thereby treating one of the diseases as recited in the claims, should be considered as the feature conferring novelty to the claims in the sense of G 5/83.

Consequently, appellants have attempted to draft claims in the format of "second (further) medical use" in all pending requests. In particular, claims 1 of the main request and the fourth auxiliary requests, claim 2 of the second auxiliary request, and claims 1 of the first and third auxiliary request in conjunction with the respective claims 2 of said first and third auxiliary requests, are drafted in that manner.

2.5 Having regard to the above mentioned decisions of the Enlarged Board of Appeal, the structure of such a "Swiss - type" claim contains the following essential elements:

- (a) the use of a compound or composition;
- (b) for the manufacture of a medicament;
- (c) for a therapy.

2.6 While conditions a) and c) are doubtlessly satisfied in the claims under examination, the Board is not convinced that condition b) is met, and more

specifically, that the claims indeed relate to the manufacture of a medicament, for the following reasons.

The Board accepts the appellant's argument that the adsorbent is changed during its use, the specific cytokine interacting therewith and being retained thereon. It is thus, for all practical purposes, consumed during the treatment of the body fluid and differs, in this respect, from a surgical tool. The appellant has referred to T 227/91 where it is said under Reasons, point 5.2, that medicaments are consumed during their use and hence useable only once, in contrast to a surgical use of an instrument which may be re-used for the same or even a different purpose. However, from the above statement it cannot be derived that every tool, substance or composition which is consumed during its therapeutic use is a medicament.

The appellant defined a medicament as a substance (or composition) which is applied to a patient in order to treat a disease.

The Board does not consider it necessary to enter into a fully - fledged discussion of possible definitions for the term "medicament". In the instant case, it turns out that the adsorbent used in accordance with the present application does not meet at least one essential characteristic of a medicament; the question of whether it would meet or not meet still other characteristics is therefore moot.

In the Board's view, an essential characteristic of a medicament is that it be administered to a patient's body in order to treat a disease. This means that the

medicament is brought into contact with the body in order to deliver and apply a substance or composition in an effective form and dose for it to develop its therapeutic effects within the patient's body. It is evident that the porous adsorbent of the present application does not, and for that matter cannot, be administered or applied directly to the human body. In accordance with the description (page 16, lines 31 - 36), the adsorbent is used in a cartridge or column provided with a filter element preventing the adsorbent from effusing outside of the cartridge or column when the body fluid is passed through it, this cartridge being located outside the body in an extracorporeal circulation cycle. The preferred mode of application of the adsorbent is therefore similar to that of a membrane for blood dialysis. In fact, it is preferably combined with such an artificial dialysis cycle (description, page 17, second paragraph). In the Board's view, considering the way they are used, neither the adsorbent nor a dialysis membrane are administered to the body of a patient. It was not denied by the appellant that a dialysis membrane is not a "medicament" within the meaning of G 5/83. However, in the appellant's view, the adsorbent would resemble medicaments of a certain type, for instance active carbon (*carbo medicinalis*) is an example, which are taken orally in order to adsorb toxic species in their passage through the gastrointestinal ductus. The Board can accept that substances such as active charcoal can be used as medicaments, but sees an important distinction in its application to a patient, in comparison with the adsorbent here under consideration, since the active carbon is administered to the patient

and develops its therapeutic effect within the patient's body, contrary to the present adsorbent.

It follows from the above that the adsorbent of the instant application is not a "medicament".

- 2.7 The Board has examined the question of whether G 5/83 leaves room for a broad interpretation which could encompass the adsorbent used in the present application. However, the text of G 5/83 itself does not warrant such an interpretation. Reference may be made to the Reasons, point 19; point 21, third and fifth sentences point 23; and the Order, point 2, all of which clearly refer to a "medicament" only.

It is stated in G 5/83 that "the application of this special approach to the derivation of novelty can only be applied to claims to the use of substances or compositions intended for use in a method referred to in Article 52(4) EPC". However, from the immediately preceding sentence, referring on two occasions to medicaments, it becomes evident again that this "special approach to the derivation of novelty" can be applied only to substances and compositions which are medicaments (Reasons, point 21).

- 2.8 Claim 1 of the fourth auxiliary request differs from claim 1 of the main request in that the word "adsorbent" (first occurrence) is replaced by the expression "adsorbent medicament". The Board does not consider this to be a change in substance, because the adsorbent does not become a medicament simply by calling it so. The Board observes that the appellant has not put forward arguments that the "adsorbent

medicament" as defined in the claims would be used in a manner different from an "adsorbent". The qualifier "medicament" does not in any way limit or modify the scope of the claim. It is significant that the term "medicament" is not used at all in the present application for characterising the adsorbent.

3. It follows from point 2 above that in claims 1 of the main request and of the fourth auxiliary request, in claim 2 of the second auxiliary request, and in claims 1 of the first and third auxiliary request taken in conjunction with the respective claims 2 of said first and third auxiliary requests, the feature relating to the intended use of the adsorbent is not a purpose - limiting feature within the meaning of G 5/83 which might render the claimed subject matter novel over D1, the adsorbent not being a medicament.

The remaining features of the said claims relate to the use of the same carrier and the same immobilized compound as in D1 for the manufacture of an adsorbent which is prepared in the same manner as that of D1 and hence is identical to the one of this document (see point 1 above). The subject matter of said claims therefore lacks novelty having regard to document D1 (Article 54 EPC).

Since there is no allowable request on file, the application must be refused.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

C. Vodz

M. Eberhard