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Datasheet for the decision of 22 March 2013

Case Number: T 1869/11 - 3.3.02

Application Number: 03704789.1

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Language of the proceedings: EN

Title of invention:
Use of glycosaminoglycans such as E.G. heparin for the treatment of respiratory disorders such as COPD

Patent Proprietor:
Ockham Biotech Limited

Opponent:
Vectura Limited

Headword:
Treatment of respiratory disorders/OCKHAM BIOTECH LIMITED

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2), 111

Keyword:
"New main request - admission (yes)"
"Added matter (no)"
"Sufficiency of disclosure, novelty and inventive step (yes)"
"Remittal (no)"

Decisions cited:
G 0002/08, T 0609/02

Catchword:
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Case Number: T 1869/11 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 22 March 2013

Appellant: (Patent Proprietor)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 27 June 2011 revoking European patent No. 1511466 pursuant to Article 101(3)(b) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: A. Lindner
R. Cramer

Summary of Facts and Submissions

I. European patent No. 1 511 466, based on application No. 03 704 789.1, was granted on the basis of 11 claims.

II. An opposition was filed against the patent. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step and for exclusion from patentability pursuant to Article 53(c) EPC, under Article 100(b) EPC for insufficiency of disclosure and under Article 100(c) EPC for amendments that contained subject-matter extending beyond the content of the application as filed.

III. The documents cited during the opposition and appeal proceedings included the following:

(1) J.P. Boyle, et al., Amer. J. Cardiol. (1964), vol. 14, 25-28
(3) B. Mulloy, et al., Throm. Haemost. (2000), vol. 84, 1052-1056
(4) WO 99/06025
(7) P. Youngchaiyud, et al., Am. Rev. Resp. Dis. (1969), vol. 99(3), 449-452
(8) WO 00/25723
(9) M. Ledson, et al., Eur. Resp. J. (2001), vol. 17, 36-38
(19) J. Shute, et al., abstract "Anti-inflammatory effects of inhaled nebulised heparin in adult CF patients - results of a pilot study" (2000)
(36) M Salathe, et al., Chest (1996), vol. 100, 1048-1057
(54) P.J. Barnes, J. Clin. Investig. (2008), vol. 118, 3546-3556

(62) Global Initiative for Chronic Obstructive Lung Disease, National Institutes of Health, National Heart, Lung, and Blood Institute, publication number 2701, March 2001

IV. The appeal lies from a decision of the opposition division, pronounced on 9 June 2011 and posted on 27 June 2011, revoking the European patent.

V. In said decision, the opposition division decided that claim 9 of the main request was not allowable under Article 123(2) EPC and that the claims 1 of auxiliary requests I, IV and V were not novel vis-à-vis document (1). It argued that the compound "Lipo-Hepin" disclosed therein contained heparin sodium. Moreover, it was convinced that said "Lipo-Hepin" inevitably had a molecular weight in the claimed range of 12 to 18 kilodaltons. As a consequence, this feature was implicitly disclosed in document (1). Regarding inventive step, the opposition division reasoned that the only difference between the use according to claim 1 of auxiliary request II and the method disclosed in document (1), which had been identified as the closest prior art, was the mode of administration by inhalation. Since it was well known from document (19) that heparin could be administered via inhalation, the subject-matter of claim 1 of auxiliary request II lacked an inventive step. Nor could the further definition of the mucus, which according to claim 1 of auxiliary request III contained extracellular genomic DNA, establish an inventive step. The skilled person was aware that extracellular genomic DNA was present in the mucus of CAL (chronic airflow limitation) patients,

so that the inclusion of that feature in claim 1 was not limiting.

VI. The appellant (patentee) lodged an appeal against that decision.

VII. At the oral proceedings before the board, which were held on 22 March 2013, the appellant submitted a new main request. The independent claims read as follows:

"1. Use of a glycosaminoglycan or a physiologically acceptable salt thereof in the manufacture of a medicament for facilitating the clearance of mucus from the central and peripheral airways of a human subject with chronic airflow limitation (CAL) who has mucus hypersecretion wherein the said glycosaminoglycan or salt has an average molecular weight of from l2 to 18 kilodaltons and the medicament is administered via inhalation, intranasally, and/or via installition.

9. A glycosaminoglycan or a physiologically acceptable salt thereof for use in facilitating the clearance of mucus from the central and peripheral airways of a human subject with chronic airflow limitation (CAL) who has mucus hypersecretion wherein the said glycosaminoglycan or salt has an average molecular weight of from l2 to 18 kilodaltons and is administered via inhalation, intranasally, and/or via installition."

VIII. The appellant's arguments can be summarised as follows:

Regarding the question whether or not the case should be remitted to the first instance for the evaluation of insufficiency, the appellant made reference to its

request for accelerated appeal proceedings and cited the notice from the Vice-President DG3 dated 17 March 2008 (OJ EPO 2008, 220), according to which a situation in which the decision of potential licensees of the patent in suit hinged upon the outcome of the appeal proceedings constituted a reason for accelerating the appeal proceedings. This was exactly the situation the appellant was in. The appellant was a tiny private company for which licensing, which was impeded by the uncertainty created by the opposition and appeal proceedings, was of vital importance. Regarding the absence of documentation in support of the request for acceleration, the appellant stressed that such documentation was commercially sensitive and that it preferred not to identify its potential partner. However, if needed, the appellant was ready to provide such evidence. In view of this situation, the case should not be remitted to the first instance for further prosecution.

As far as the allowability of the amendments were concerned, there was no selection from several lists. The combination of features in the independent claims of the main request constituted the core of the invention, as could be seen from the examples.

Document (7) was not detrimental to novelty, because it disclosed neither a glyosaminoglycan with a molecular weight in the range of from 12 to 18 kilodaltons nor facilitation of mucus clearance in CAL patients.

Regarding the selection of the closest prior art for the assessment of inventive step, the skilled person would dismiss documents (1) and (7) on account of their

age and choose document (36) instead, which recommended treatment of mucociliary dysfunction by a combination of drug therapy involving inhalation of ß-adrenergic agonists and physical therapy. In connection with document (1), the appellant further disputed the assertion that Lipo-Hepin® contained heparin. Reference was made to the fact that heparin was always written in quotation marks, which indicated a heparin-like substance but not necessarily heparin itself or even a glycosaminoglycan.

IX. The respondent's arguments can be summarised as follows:

Regarding the question whether or not the case should be remitted to the first instance for the evaluation of insufficiency, the appellant's request for accelerated appeal proceedings did not meet the criteria of the notice from the Vice-President DG3 dated 17 March 2008 and should therefore be refused. No documentation had been provided by the appellant in support of this request. As a consequence, any issues, such as insufficiency, that had not been addressed by the opposition division should not be considered by the board. Instead, in the event that the patent was not revoked for other reasons, the case should be sent back to the opposition division for further prosecution in order to avoid the parties only being able to argue these issues before one instance and losing the possibility to appeal.

In any case, there was insufficiency for the following reasons: for a use-limited product claim or second medical use claim, there had to be data in the original application to support the effect claimed. The

contested patent did not, however, show any effect on facilitation of mucus clearance from the central and peripheral airways of a human subject with CAL and mucus hypersecretion. Example 1 concerned sputum but did not show any effect on mucus clearance. Example 3 referred to ALD (airflow limitation disease) and not CAL with mucus hypersecretion. Furthermore, no evidence had been provided in the patent in suit regarding glycosaminoglycans other than heparin to show the desired effect. In addition, there was no information as to the molecular weight of the heparin used in the examples or as to how the molecular weight was measured. Nor did the patent in suit contain any evidence to support the assertion that clearance of mucus was facilitated by a change of the mucus's viscosity.

Document (7) comprised all features of the independent claims of the main request, as the heparin used therein mandatorily had a molecular weight in the range of from 12 to 18 kilodaltons. As a consequence, the main request lacked novelty.

The age of documents was not relevant for consideration of inventive step. Document (1) was the closest prior art as it also addressed the use of a glycosaminoglycan for facilitating mucus clearance in CAL patients with mucus hypersecretion. The average molecular weight of the heparin was not implicitly disclosed in document (1), so that the administration by inhalation, intranasally or by instillation constituted the only difference. As a consequence, finding an appropriate delivery route for the glycosaminoglycan could be defined as the problem to be solved. On the effective

filing of the patent in suit, the skilled person would find it obvious to try inhalation. Furthermore, document (19) stated that inhaled unfractioned heparin had been shown to improve lung function in COPD (chronic obstructive pulmonary disease). The fact that document (19) focused on the anti-inflammatory effect of heparin in CF (cystic fibrosis) patients was irrelevant, as inflammation and particularly neutrophil elastase from neutrophils, the predominant inflammatory cell in both COPD and CF, was a key driver of mucus hypersecretion in COPD and CF, and therefore any anti-inflammatory effect of heparin was likely to also increase the specific mucolytic/mucus-reduction effects of heparin in these patients. Reference was made to documents (54) and (62) in this context. In addition, there were further documents such as documents (4) and (8), envisaging inhalation as a preferred administration route for heparin. Document (9) confirmed the mucolytic effects of heparin and pointed to the advantages of inhalation over other delivery routes.

Moreover, the respondent argued that the appellant had not shown any technical effect associated only with the molecular weight range specified in claim 1, which was not even mentioned in the examples of the patent in suit.

X. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed at the oral proceedings or alternatively on the basis of one of the auxiliary requests 1-4 filed with the grounds of appeal. The

appellant further requested that, if applicable, the board also consider sufficiency of disclosure.

The respondent requested that the appeal be dismissed. It further requested that, if the decision under appeal be set aside, the case be remitted to the department of first instance for the prosecution of any issues that had not been addressed by the opposition division in the decision under appeal.

Reasons for the Decision

1. The appeal is admissible.

2. Procedural matters

2.1 Admission of the main request

This request was filed at the oral proceedings before the board and therefore at a very late stage of the appeal proceedings. Its admission is therefore at the board's discretion and depends upon the overall circumstances of the case under consideration, including the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy.

The present main request differs from the previous main request, submitted with the statement of the grounds of appeal, by the deletion of dependent claims 4 and 6. This amendment, which is of a simple nature as it did not concern the independent claims at all, was the consequence of the board's conclusion, drawn at the

oral proceedings, that these claims were not allowable under Article 123(2) EPC. The respondent could not have been taken by surprise by this deletion. As a consequence, this amendment is admissible (Article 13(3) RPBA).

In addition, compared to claims 1 and 11 as granted, independent claims 1 and 9 of the present main request comprise the additional feature "and the medicament is administered via inhalation, intranasally, and/or via instillation" [spelling correction by the board]. This feature had already been introduced into claims 1 and 11 of the previous main request filed with the statement of the grounds of appeal and objected to by the respondent in its reply dated 20 March 2012 to the statement of the grounds of appeal (see point 1.2 of the reply). According to Article 12(4) RPBA, it is within the discretionary power of the board to hold inadmissible facts, evidence or requests which could have been presented or were not admitted in the first-instance proceedings. In the present case, the board notes that similar requests, in which intranasal administration was included in the independent claims, had already been submitted in the opposition proceedings as auxiliary requests 2 and 3 and dealt with in the decision under appeal (see pages 9 and 10). As a consequence, the present main request was not deliberately withheld in order to avoid a decision on the part of the opposition division.

Moreover, inhalation, instillation and intranasal administration constitute the most preferred embodiments of the present application in view of the disclosure on page 28, line 31 to page 29, line 2 of

the present application, and in view of the fact that they are the only modes of administration specifically mentioned in the original claims (see claims 10 and 17 of the original application). As a consequence, their introduction into claims 1 and 9 of the present main request was foreseeable.

The present main request is therefore admitted into the proceedings.

2.2 Remittal for the examination of insufficiency

The ground for opposition pursuant to Article 100(b) EPC had already been cited and substantiated in the notice of opposition. The opposition division did not, however, decide on this issue. Under Article 111(1) EPC, whether the board itself decides an issue, or whether it refers the matter back to the first instance for decision, is within the discretion of the board. Parties do not have a right to have each issue decided by two instances. Whereas at an early stage of the proceedings the board usually exercises its discretion to remit the matter to the first instance for further prosecution, in cases such as the present one, where remittal and the resulting prolongation of the proceedings would be disadvantageous for the appellant, the position is different. Moreover, the objections had already been raised in the notice of opposition (see pages 41-47). No new objections had been raised in the course of the appeal proceedings. The board therefore decided not to remit the case to the first instance and to deal with insufficiency of disclosure itself.

3. Main request

3.1 Amendments

3.1.1 As compared to claim 1 of the original application, claim 1 of the present main request comprises the following additional features:

(a) for facilitating the clearance of mucus
(b) from the central and peripheral airways
(c) of a human subject
(d) who has mucus hypersecretion
(e) from 12 to 18 kilodaltons
(f) the medicament is administered via inhalation, intranasally, and/or via instillation.

3.1.2 As a first step, it has to be determined whether or not these or some of these features are correlated.

3.1.2.1 Starting with feature (d), the board notes that CAL including mucus hypersecretion is selected from seven symptoms listed on page 14, lines 18-21 of the original application, of which mucus hypersecretion and ciliary dysfunction are further highlighted in lines 22-23 of the same page. Furthermore, all three examples are related to mucus or its treatment. Example 1 involves an *in vitro* test demonstrating the mucolytic effect of heparin. Example 2 and corresponding figures 2 and 3 concern microscopic images of an *in vitro* assay showing structural changes of a DNA network affected by heparin. Extracellular DNA is considered to increase the viscosity of the mucus and thus to impede its clearance. Finally, example 3 describes an *in vivo* test in which the administration of heparin improved clearance of sputum. The board concludes therefrom that CAL

involving mucus hypersecretion constitutes by far the most preferred of the seven symptoms mentioned above.

3.1.2.2 Feature (a), which is disclosed in the paragraph bridging pages 25 and 26 of the original application, is closely linked to CAL involving mucus hypersecretion and can therefore not be regarded as a selection from a different list of four constituents figuring on page 25, lines 20-25 of the original application. The respondent's argument that the passage on page 25, lines 30-31 of the original application "The medicaments and methods of the invention **may** facilitate the clearance of mucus" [emphasis by the board] is speculative, and can therefore not form the basis of that amendment, cannot be followed. Reference is again made to example 3 which disproves the alleged speculative character of mucus clearance.

3.1.2.3 Feature (b) is disclosed on page 13, lines 23-25 of the original application, where central airways, peripheral airways, lung parenchyma and/or pulmonary vasculature are mentioned as sites for pathological changes characteristic of CAL. However, as was correctly pointed out in the decision under appeal (see point 2.1.7 of the Reasons for the decision), once mucus hypersecretion is selected as the symptom to be treated, the central and peripheral airways will mandatorily constitute the site of said pathological changes, as no mucus is produced or located in the pulmonary vasculature and those parts of the lung parenchyma which may contain mucus are included in the term "central and peripheral airways".

The board notes that the four sites of pathological changes characteristic of CAL on page 13, lines 23-25, are linked by "and/or", which according to the respondent leads to further possible selections. This would mean that even if lung parenchyma and pulmonary vasculature were excluded as sites for mucus hypersecretion, feature (b) would still have to be selected from the three options of central airways (b1), peripheral airways (b2) and central and peripheral airways (b3). However, such a differentiation would apply only if there were patients where mucus was solely located in the central airways, other patients where it could be found only in the peripheral airways, and a further subset of patients with mucus in both the central and peripheral airways. Such a distinction is, however, purely academic and of no practical relevance. The difference between central and peripheral airways, as was explained by the appellant, is their diameter which is >2 mm in central airways and <2 mm in peripheral airways. This definition was not contested by the respondent. The presence of mucus only in the peripheral airways and its absence in the central airways and *vice versa* is not plausible and has not been substantiated by any evidence.

3.1.2.4 The board therefore concludes that features (a), (b) and (d) are dependent on each other, which means that only one selection, namely CAL with mucus hypersecretion (feature (d)), has to be made and that addition of features (a) and (b) is the logical consequence of said selection.

3.1.3 Regarding feature (c), it is noted that the present invention is predominantly directed to human patients. The board is aware of the fact that the original application also discloses treatment of non-human patients (see page 3, lines 25-27, page 15, lines 3-19, and claims 14 and 15 of the original application), but only as a hypothetical option. The preferred target group is humans and in particular smokers or ex-smokers (see page 1 of the original application). As a consequence, the selection of human subjects cannot be regarded as a selection from a further list.

3.1.4 As regards feature (e), reference is made to the passage on page 16, lines 23-28 of the original application which discloses a series of preferred molecular weight ranges for glycosaminoglycans, including 12 to 20 kilodaltons, 14 to 18 kilodaltons, 15 to 17 kilodaltons and 16 to 17 kilodaltons. The board notes that the claimed range of 12 to 20 kilodaltons is not specifically disclosed in that passage but has to be derived by combining the lower end of the range 12 to 20 kilodaltons with the upper end of the range 14 to 18 kilodaltons. However, said range of 12 to 18 kilodaltons obtains the status of a highly preferred embodiment by the fact that it is the only molecular weight range figuring in the original claims (see claim 7 of the original application).

3.1.5 Feature (f) is disclosed in the sentence bridging pages 24 and 25 in claims 10 and 16 of the original application. As no other route of administration is contemplated therein, the addition of feature (f) does not constitute a selection from a further list.

3.1.6 In summary, features (a), (b) and (d) are dependent on each other, involving as sole selection the selection of feature (d) out of a list of seven constituents, features (c) and (e) are by far the most preferred embodiments of their category and feature (f) represents the only embodiment of its category. As a consequence, the subject-matter of claim 1 of the main request meets the requirements of Article 123(2) EPC.

3.1.7 The reasoning of points 3.1.1 to 3.1.6 above applies *mutatis mutandis* to the subject-matter of claim 9, which therefore also meets the requirements of Article 123(2) EPC.

3.2 Insufficiency

3.2.1 The independent claims of the present main request are formulated as a Swiss-type claim (claim 1) and as use-limited product claim (claim 11), where attaining the claimed therapeutic effect is a functional feature of the claim. As a consequence, the patent in suit must disclose the suitability of the product as defined in claim 9 or as to be prepared according to claim 1 for obtaining said therapeutic effect. The respondent, making reference to decision T 0609/02, pointed out that it was required that the patent provide some information in the form of, for example, experimental tests, to show that the claimed compound had a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism either being known from the prior art or demonstrated in the patent per se.

3.2.2 The board notes that example 3 of the contested patent describes the treatment of a female patient, ex-smoker,

with ALD, who inhaled unfractioned heparin at a dose of 50,000 units twice a day for 14 days. Although there was no change in spirometry over this short period, there was a marked improvement in symptoms of cough, and improved clearance of sputum. The skilled person would deduce that ALD means airflow limitation, which he would identify as a synonym for CAL. Example 3 of the contested patent shows that heparin facilitates the clearance of mucus in a CAL patient with mucus hypersecretion. Example 3 does not mention that the mucus is located in the central and peripheral airways, which is, however, not necessary as the skilled person would expect it there (see point 3.1.2.3 above). Nor is the fact that example 3 does not specifically mention the molecular weight of the unfractionated heparin of any consequence for insufficiency in this case. The original application teaches that any glycosaminoglycan, of which heparin is particularly preferred, with a molecular weight in the range of 8 to 40 kilodaltons achieves the desired effect (see paragraph bridging pages 2 and 3 and page 24, lines 4-5 of the application as filed). Example 3 is representative of this original teaching. This means that the molecular weight of the heparin used therein was within that broad range of 8 to 40 kilodaltons but not necessarily within the range of from 12 to 18 kilodaltons as claimed in the present main request. However, in view of the fact that the molecular weight range of 12 to 18 kilodaltons constitutes a highly preferred embodiment (see point 3.1.4 above), the board has no doubts that the effect demonstrated in example 3 is representative of the molecular weight range now claimed. In this context, the board wishes to point out that the patentee is not required to reveal the mechanism of action behind the

desired effect. To meet the requirements of Article 83 EPC, it is sufficient that the achievement of the effect is made plausible.

3.2.3 Regarding the respondent's objection that the application as filed does not disclose a method for determining the molecular weight of the glycosaminoglycan, the board notes that in a case like this, where a considerable number of commercial products are available, the skilled person is not required to prepare the glycosaminoglycan in order to carry out the claimed invention. Commercial products are usually described by various parameters, including molecular weight, so that the absence of such a method in the application as filed does not lead to insufficiency.

3.2.4 As far as the respondent's objection that no evidence had been provided in the patent in suit regarding glycosaminoglycans other than heparin to show the desired effect, the board wishes to emphasise that sufficiency of disclosure must be evaluated in the light of the entire disclosure. Example 3 shows, as was mentioned above, that heparin achieves facilitation of mucus clearance from the central and peripheral airways. Example 1, which relates to an *in vitro* assay, shows that heparin and a second glycosaminoglycan, namely chondroitin sulphate, reduce the viscosity of the mucus. Although, as was correctly pointed out by the respondent, this assay does not demonstrate an enhanced clearance of mucus from the central and peripheral airways, the skilled person would regard the reduction of the mucus's viscosity as a pointer towards a facilitated clearance.

3.2.5 In view of this information to be found in the application as filed, the board is satisfied that the invention can be carried out over essentially the entire range of the claims. As a consequence, the requirements of Article 83 EPC are met.

3.3 Novelty

3.3.1 Preliminary remark

In the subsequent evaluation of novelty and inventive step, the symptoms chronic airflow limitation (CAL) and chronic obstructive pulmonary disease (COPD) are regarded as synonymous.

3.3.2 Document (7) discloses treatment of patients suffering from COPD via inhalation of aerosolised heparin (see page 449, paragraph bridging the left-hand and right-hand columns). Document (7) does not further specify the heparin used for that treatment. In particular, there are no indications concerning its molecular weight. The respondent's argument that the required molecular weight range of 12 to 18 kilodaltons was implicitly disclosed in the light of document (3) cannot be followed. Document (3), which is a review article about heparin, describes heparin products available during the past 50 years. Table 3 lists the mean molecular weights of a variety of preparations including US Pharmacopoeia K3 and K4, which are all within the claimed range of 12 to 18 kilodaltons. Document (3) indicates a certain probability for the heparin used in document (7) to have a molecular weight of 12 to 18 kilodaltons, which is, however, not

sufficient to destroy the novelty of the claimed subject-matter.

3.3.3 In view of the limitation of the subject-matter of the present main request to inhalation, intranasal administration and instillation, document (1), which discloses intravenous administration of heparin, is no longer relevant for novelty. In addition, document (1) does not disclose the molecular weight of heparin, either explicitly or implicitly in the light of document (3) (see point 3.3.2 above).

3.3.4 As a consequence, the subject-matter of the main request meets the requirements of Article 54 EPC.

3.4 Main request - inventive step

3.4.1 The present invention concerns facilitation of the clearance of mucus from the central and peripheral airways of patients suffering from CAL and mucus hypersecretion.

3.4.2 Regarding the closest prior art, the board notes that document (36), which the appellant had proposed as closest prior art, recommends treatment of mucociliary dysfunction by a combination of drug therapy involving inhalation of ß-adrenergic agonists and physical therapy (see conclusions on page 1054). In view of this teaching, document (36) is not a suitable starting point for the assessment of inventive step. Instead, the closest prior art has to be selected from documents (1) and (7). Both documents were published almost 50 years ago, which however does not mandatorily exclude them as closest prior art. There may be various

reasons why a certain initially promising line of research is not continued. One reason is of course subsequent lack of performance, in which case the skilled person would indeed disregard such an old document. But there are other factors not related to product performance which might make a company decide to discontinue a research project, such as economic, strategic or political considerations, in which case a document published long ago can still be of considerable interest to the skilled person. The publication date of a prior-art document is certainly a factor that has to be taken into consideration in the assessment of inventive step, but dismissing a document only because it was published a relatively long time ago, without looking at its content at all, would not guarantee a fair and unbiased evaluation of the prior art, in particular in a situation where, like in the present case, an old but pertinent document would be replaced by a document published more recently but whose technical teaching is completely irrelevant.

3.4.2.1 As already mentioned in point 3.3 above, document (7) does not specifically mention a molecular weight range of 12 to 18 kilodaltons for heparin. Moreover, it has to be evaluated whether or not it discloses facilitation of mucus clearance. The sentence bridging the two columns on page 449 lists the following two possible beneficial effects in patients with COPD following inhalation of a heparin aerosol: (a) removal of secretions from the airways (= facilitation of mucus clearance) and (b) bronchial dilatation secondary to either an antihistamine or antiserotonin action. These effects are at that point hypothetical and are subsequently tested in a clinical trial. The first

complete paragraph on the right-hand column of page 449 defines two groups of patients of which group (B) concerns patients suffering from COPD with a long history of breathing difficulty, cough and expectoration and a grossly abnormal ventilatory function. The board concludes that the pathological symptoms of this patient group correspond to the symptoms to be treated according to present claim 1, i.e. CAL in combination with mucus hypersecretion. In document (7), the following aerosol compositions were used for the tests: (a) saline, (b) vehicle (= 0.5% phenol), (c) heparin dispersed in 0.5% phenol, and (d) isoproterenol. Figure 1 shows that inhalation of aerosol composition (c) leads to a significant change in specific conductance which is much more pronounced than the changes observed with compositions (a) or (b). However, with regard to sputum expectoration, which is an indication for the facilitation of the clearance of mucus, the board notes that no significant changes can be observed between compositions (b) and (c). Reference is made to table 2 which notes a sputum weight of 3.1 ± 3.4 g for composition (b) and of 3.4 ± 3.9 g for composition (c). This means that there is overlap at 3.4 g and no statistically significant difference between heparin dispersed in vehicle and vehicle alone. There is, however, a statistically significant difference between composition (b) or (c) on the one hand and composition (a) on the other hand, with a sputum weight of 1.4 ± 2.0 g. The board concludes from these values that phenol facilitates mucus clearance, but no such effect can be observed with heparin. In summary, document (7) shows that heparin, if administered by inhalation, does not facilitate mucus

clearance in CAL patients having mucus hypersecretion, and therefore does not qualify as closest prior art.

3.4.2.2 Document (1) concerns a clinical study in which Lipo-Hepin® was intravenously administered to patients suffering from either a "status asthmaticus" (group A) or severe chronic bronchopulmonary disease with respiratory distress due to bronchospasm or tenacious secretions, or both (group B) (see page 25). The board has no doubts that Lipo-Hepin® contains heparin. Reference is made to the second sentence of the first paragraph of "Materials and Methods" on page 25, which reads: "Both heparin, as Lipo-Hepin®, and placebo were provided by Riker Laboratories"). The fact that heparin is cited in quotation marks (see right-hand column of page 25) can be explained by the fact that document (1) concerns a double-blind study in which either sodium heparin or a placebo was administered but all samples were labeled "Heparin, Sodium U.S.P. 20,000 units/cc.". This does not, however, justify the appellant's conclusion that Lipo-Hepin® does not contain heparin.

The results of this study are, however, not entirely unequivocal. On the one hand, a beneficial effect is attributed to heparin in eliminating obstructing secretions in patients with chronic obstructive bronchopulmonary disease (see first paragraph of the right-hand column on page 27). On the other hand, the authors of document (1) conclude that it is difficult to assess to what degree heparin therapy has contributed thereto (see fourth paragraph of the right-hand column on page 27).

3.4.3 However, in view of the overall disclosure of document (1), including the Case 2 study in the right-hand column of page 26, the skilled person would conclude that the mucolytic effect can indeed be attributed to heparin. As a consequence, document (1) constitutes the closest prior art and the problem to be solved can be defined as the provision of an alternative administration form for heparin for facilitating the clearance of mucus from the central and peripheral airways of a CAL patient with mucus hypersecretion.

3.4.4 The proposed solution to this problem concerns administration of a glycosaminoglycan with an average molecular weight of form 12 to 18 kilodaltons via inhalation, intranasally or via instillation.

3.4.5 Regarding the question whether or not the problem has been plausibly solved, reference is made to the examples, in particular examples 1 and 3 (see also points 3.2.2 to 3.2.4 above. Furthermore, the board considers administration via inhalation (see example 3) to be representative of the related forms instillation and intranasal administration. As a consequence, the board concludes that the problem has indeed been plausibly solved.

3.4.6 The skilled person gets no incentive from document (1) to administer a glycosaminoglycan in the way claimed in the present main request. The skilled person would therefore turn to document (7) in which heparin is administered via inhalation. However, for the reasons outlined in point 3.4.2.1 above, the skilled person would not conclude from the disclosure of document (7)

that heparin administered via inhalation facilitates the clearance of mucus. The board is aware of the last complete sentence of the left-hand column of page 449 which reads: "The present writers observed that inhalation of aerosolized heparin precipitated expectoration". This sentence has, however, to be read in the context of the whole disclosure of document (7). Aerosolised heparin therein means heparin dispersed in phenol. Reference is again made to point 3.4.2.1 above, in which it is explained that the improved clearance of mucus has to be attributed to phenol. No such effect can be derived from heparin.

Nor can this information be retrieved from document (19) which discloses inhalation of heparin in order to improve lung function in a number of airway diseases including allergic asthma and COPD. Anti-inflammatory activity, in particular in connection with patients suffering from CF, is mentioned. Although the skilled person learns from document (19) that inhalation of heparin may be beneficial in the treatment of COPD in general, he gets no information that such treatment facilitates the clearance of mucus in CAL patients with mucus hypersecretion. The respondent's argument that inflammation was known to be a key driver of mucus hypersecretion in COPD and CF, so that the skilled person would expect any anti-inflammatory effect of heparin to very likely also increase facilitation of mucus clearance in the patient group defined in the present claims, cannot be followed in the light of the results of document (7), where no facilitation of mucus clearance was observed in CAL (=COPD) patients upon heparin administration via inhalation. The skilled person would therefore deduce

that the mucolytic effect of heparin upon administration via inhalation was dependent on the specific disease and that mucus clearance in CAL patients by means of heparin or glycosaminoglycan in general required administration modes other than inhalation.

For the same reason, documents (4), (8) and (9), which do not relate to CAL patients, are not relevant either. The teaching that inhalation may constitute the preferred administration mode for heparin for facilitating mucus clearance in certain diseases cannot be transferred to CAL patients in the light of document (7).

As a consequence, the subject-matter claimed in the present main request is not rendered obvious by the available prior art, so that the requirements of Article 56 EPC are met.

3.5 The further ground for opposition cited in the notice of opposition under Article 100(a) EPC, namely the exclusion from patentability pursuant to Article 53(c) EPC, was not maintained in the appeal proceedings and is no longer relevant in view of decision G 02/08 (OJ EPO 2010, 456), which has been published in the meantime.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of the main request filed during the oral proceedings, and a description to be adapted thereto.

The Registrar: The Chairman:

N. Maslin U. Oswald