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D E C I S I O N
of 12 October 1999

Case Number: T 0138/95 - 3.3.4

Application Number: 87307276.3

Publication Number: 0257956

IPC: A61M 15/00

Language of the proceedings: EN

Title of invention:
Device and dispersion for intrapulmonary delivery of polypeptide growth factors and cytokines

Patentee:
GENENTECH, INC.

Opponent:
Schering Corporation

Headword:
Intrapulmonary delivery/GENENTECH INC.

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"Main request: novelty (yes) - new method of drug administration - inventive step (yes)"

Decisions cited:
G 0005/83, G 0002/88, T 0051/93

Catchword:

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0138/95 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 12 October 1999

Appellant: (Opponent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 13 December 1994 concerning maintenance of European patent No. 0 257 956 in amended form.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: R. E. Gramaglia
W. Moser

Summary of Facts and Submissions

I. European patent No. 0 257 956 (application No. 87 307 276.3) was granted on the basis of 17 claims. Independent claims 1 and 9 as granted read as follows:

"1. A device for delivering to the blood stream of a patient a therapeutic dose of a polypeptide selected from growth factors and cytokines, said device comprising reservoir means (8) for storing the polypeptide; a therapeutic dosage form of the polypeptide disposed in the reservoir means; dispersing means (4-7) for forming in a gas a suspension of particles comprising the polypeptide wherein greater than about 15% of the particles have a mean average diameter of about from 0.5 μm to 4 μm; means (1-3) for transporting the polypeptide to the dispersing means and means (9-12) for delivering the particle suspension to the alveoli of the patient's lungs.

9. A dispersion of polypeptide containing particles wherein greater than about 15% of the particles have a mean average diameter of about from 0.5 to 4 μm and wherein the polypeptide is selected from growth factors and cytokines."

Claims 2 to 8 and 10 to 17 were directed to specific embodiments of the devices of claim 1 and the dispersion of claim 9, respectively.

II. Notice of opposition was filed by the appellant (opponent). Revocation of the patent in its entirety was requested on the grounds of Article 100(a) EPC, ie lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC).

III. By its decision given orally and issued in writing on 13 December 1994, the opposition division maintained the patent in amended form on the basis of claims 1 to 19 of the main request submitted at the oral proceedings. The following documents are referred to in the present decision:

(1) Wigley F. M. et al., Diabetes, Vol. 20, pages 552-556 (1971);

(4) Wyde P. R. et al., Antimicrobial Agents and Chemotherapy, Vol. 25, pages 729-734 (1984);

(18) Juliano R. L., Pharmacology and Therapeutics, Vol. 24, pages 355-365 (1984);

(19) Egan E. A., J. Appl. Physiology, Vol. 53, pages 121-125 (1982);

(31) Ho K. Y. et al, Journal of Clinical Endocrinology and Metabolism, Vol. 64, pages 51-58 (1987).

IV. The appellant (opponent) filed a notice of appeal against this decision and a Statement of Grounds of Appeal. The respondent (proprietor of the patent in suit) filed counterarguments together with a main claim request and auxiliary claim requests A to F. With the respondent's letter dated 21 September 1999, auxiliary claim requests A to L were also submitted.

V. The appellant was not represented at the oral proceedings held on 12 October 1999, during which the respondent filed a new main request in replacement of any preceding main requests, which was identical with auxiliary request A filed by the respondent with the letter dated 21 September 1999.

Claims 1 and 9 of this main request read as follows:

"1. Use of a polypeptide selected from growth factors and cytokines for the manufacture of a device for delivering to the blood stream of a patient a therapeutic dose of the peptide by systemic delivery by pulmonary absorption said device comprising reservoir means (8) for storing the polypeptide; a therapeutic dosage form of the polypeptide disposed in the reservoir means; dispersing means (4-7) for forming in a gas a suspension of particles comprising the polypeptide wherein greater than about 15% of the particles have a mean average diameter of about from 0.5 μm to 4 μm; means (1-3) for transporting the polypeptide to the dispersing means and means (9-12) for delivering the particle suspension to the alveoli of the patient's lungs."

"9. Use of a polypeptide selected from growth factors and cytokines for the manufacture of a dispersion of said polypeptide for delivering to the blood stream of a patient a therapeutic dose of the polypeptide by systemic delivery by pulmonary absorption, said dispersion containing particles wherein greater than about 15% of the particles have a mean average diameter of about from 0.5 to 4 μm."

Claims 2 to 8 and 10 to 17 were directed to specific embodiments of the medical use of claims 1 and 9, respectively.

VI. The appellant submitted in writing essentially the following arguments:

Novelty

- Document (1) related to a study of the transport of insulin, ie a growth hormone, across the respiratory mucosae by aerosol delivery. Insulin was aerosolized by using a "Devilbiss No. 40" nebulizer which produced particles with a mean size of 2 μm. Therefore it was inevitable that greater than about 15% of the particles would have exhibited a mean average diameter of about from 0.5 to 4 μm as stated in claim 1.

- Document (4) related to pulmonary deposition and clearance of aerosolized interferon, ie a cytokine. The "Collison" nebulizer disclosed by this document was said to generate particles having a size ranging from 0.6 μm to 6.6 μm with more than 90% of the particles having a size of less than 5.0 μm. It was inevitable that greater than about 15% of the particles would have exhibited a mean average diameter of about from 0.5 to 4 μm as recited in claim 1.

- Therefore, documents (1) and (4) anticipated the claimed medical uses.

Inventive step

- If the problem to be solved by the patent in suit in the light of documents (1) and (4) was to provide therapeutic doses of polypeptides by intra pulmonary absorption, then the Examples of the patent in suit did not show any therapeutic efficacy. In Example 1, the claimed use achieved only 0.28 μg/ml, namely only 1/10th of the normal detectable level of growth hormone (GH) which is 10-20 μg/ml. Example 2 was even less relevant since it related to the intra tracheal

instillation of γ-interferon or tumor necrosis factor (TNF) to rats, ie these cytokines were not administered in the form of a gas suspension of particles.

- Documents (1) and (4) showed a therapeutical effect of the growth factor (insulin) or cytokine (interferon) when administered as an aerosol. Although the blood levels were low, the skilled person would have used larger dose of the medicament in order to achieve therapeutic levels thereof.

VII. The respondent submitted in writing and at the oral proceedings essentially the following arguments:

Novelty

- None of the prior art documents disclosed the use of a growth factor or a cytokine in the manufacture of a device for delivering to the blood stream of a patient a therapeutic dose of these polypeptides by systemic delivery by pulmonary absorption. Neither document (1) nor (4) disclosed therapeutically effective levels of the administered protein in the bloodstream arrived there by pulmonary absorption. These documents also did not teach that the small amount of protein appearing in the bloodstream arrived there by pulmonary absorption.

Inventive step

- At the priority date of the patent in suit there was a general belief in the art that large molecules such as proteins could not be absorbed through the lung's air blood barrier (see documents (18) and (19)).

- Document (1) showed that when insulin was administered by aerosol, some insulin arrived in the bloodstream, although the route by which it arrived there was unclear. Document (4) mentioned the rare occurrence of detectable interferon in blood of mice living in an aerosol of interferon. Also in this case the level were not therapeutic and the route by which it arrived in blood was not clear. By contrast, the results set out in the patent in suit demonstrated that when growth factors and cytokines were introduced into the lung (alveoli) they could be taken into the bloodstream at therapeutically effective levels.

VIII. The appellant requested that the decision under appeal be set aside and that the European patent No. 0 257 956 be revoked.

The respondent requested that the decision under appeal be set aside and that the patent be maintained on the basis of the following documents:

(a) main request: claims 1 to 17 submitted during oral proceedings; or one of

(b) auxiliary claim requests B to L filed on 21 September 1999.

Reasons for the Decision

1. The appeal is admissible.

Main request

Article 123(2) and (3) EPC

2. Independent claim 1 of the main request is drafted in the "second/further medical use" format (see decision G 5/83, OJ EPO 1985, 64), ie the "polypeptide selected from growth factors and cytokines" is to be used for the manufacture of a medical device enabling its administration to patients via the intra pulmonary route. Independent claim 9 of this request is also drafted as a second/further medical use of this polypeptide for the manufacture of a medicament in the form of a dispersion to be administered to patients via the intra pulmonary route. These claims find a basis in the application as filed (see eg page 6, lines 20 to 21 and page 1, lines 12 to 21), wherein it is stated that the only intended use of the polypeptide should occur in the medical field in the form of a dispersion to be administered by means of a device to patients via the intra pulmonary route. Dependent claim 2 finds a basis in the description on page 10, lines 11 to 12 of the application as filed. Dependent claims 3 to 8 and 10 to 17 find a basis in dependent claims 3 to 8 and 10 to 17 as filed. Further, the change of category from product claims to use claims does not broaden the scope of the claims (see decision G 2/88; OJ EPO 1990, 93). Therefore, no objection under Article 123(2) and (3) arises.

Novelty

4. The appellant argues that the particles comprising the growth hormone insulin produced by the "Devilbiss No. 40" nebulizer of document (1) or the particles comprising interferon (ie a cytokine) produced by the "Collison" nebulizer disclosed by document (4) would inevitably exhibit the size distribution stated in claims 1 and 9 and thus document (1) or (4) anticipate the claimed medical uses.

However, the board observes that the claims are now drafted in the form approved in decision G 5/83 (loc. cit.). Therefore, the intended use is a technical feature to be taken into account when assessing novelty. The intended use of the "polypeptide selected from growth factors and cytokines" is for the manufacture of a medical device enabling the administration of a therapeutic dose thereof to patients by systemic delivery by pulmonary absorption (claim 1) or for the manufacture of a medicament in the form of a dispersion to be administered in a therapeutic dose to patients by systemic delivery by pulmonary absorption (claim 9).

5. Compared with the disclosure of document (1), these claimed medical uses differ therefrom by two features: Firstly, no therapeutic level is obtained in the former document (see page 556, l-h column, second full paragraph: "the delivery of insulin by the aerosol route was of low efficiency") and thus no "therapeutic dose" of the growth factor is administered. Secondly, the way of administration of a drug is a distinguishing feature for the purpose of assessing the novelty of a medical use (see decision T 0051/93 of 8 June 1994, point 3.1.2). The administration of insulin takes place according to page 552, r-h column, lines 21 to 21 of document (1) by inhalation. The document does not

disclose whether the human patients inhalated the aerosol through their noses, mouths or both. In the board's view, the term "mucosae" in the plural to be found in the expression "crossed the **mucosae** of the respiratory tract" (emphasis added; page 555, l-h column) suggests that a significant absorption of the drug might have occurred through the nasal and/or the oral mucosae. Therefore, document (1) does not **unambiguously** teach to deliver the drug by "systemic delivery by pulmonary absorption" as stated in claims 1 and 9. Thus, these two features render claims 1 and 9 novel over document (1).

6. The conclusion arrived at by the board in respect of document (1) also applies mutatis mutandis to the disclosure of document (4), wherein also no therapeutic levels of interferon is achieved (see page 732, bottom of r-h column: "Sera from these animals ...only rarely had antiviral activity attributable to rIFN.") for interferon aerosols administered to mice held for 24 hours in plastic cages with sealed-on plastic tops (page 730, r-h column).

7. In conclusion, the novelty of the medical uses of claims 1 and 9 and dependent claims 2 to 8 and 10 to 17 has to be acknowledged.

Inventive step (Article 56 EPC)
Closest prior art

8. The board views document (1), published 1971, as representing the closest prior art, because it relates to investigations on the transport of insulin (a growth factor) across the respiratory mucosae by aerosol delivery to human patients. Although document (4) constitutes a good background, it is more remote than document (1) since it discloses interferon aerosols

administered to mice held for 24 hours in plastic cages with sealed-on plastic tops. However, insulin administered according to the experiments described in document (1) turned out to reach the bloodstream with very low efficiency, so that the disclosure of document (1) did not lead to any insulin formulation for aerosolized delivery since 1971.

Problem to be solved and its solution

9. The problem the patent in suit purports to solve is to investigate what went wrong with the experiments carried out according to document (1) in order to turn an unsuccessful test into an efficient method of therapy, wherein the right therapeutic dose of growth factor or cytokine is delivered to the patient's bloodstream. This problem is solved by the medical uses of claims 1 and 9 of the patent in suit, which achieve therapeutic levels of the polypeptides in the patient's bloodstream upon delivery by intra pulmonary absorption.

10. The appellant maintains that the patent in suit fails to solve the above problem because the Examples thereof do not show therapeutic doses of the administered growth factors or cytokines reaching the bloodstream. It is argued that in Example 1, the claimed use achieves only 0.28 µg/ml of growth hormone (GH), namely only 1/10th of the normal detectable level of GH which is 10-20 µg/ml. The board, however, accepts that the normal detectable level of growth hormone in blood is of the order of the tens of ng/ml (see document (31), Fig. 2 on page 54). Thus, Example 1 of the patent in suit shows that a therapeutic level of GH is actually achieved by the claimed medical uses. There is also no evidence before the board that by following the teaching of Example 2, therapeutic levels of γ-interferon or TNF are not obtained. The appellant

argues that Example 2 is not relevant to the claimed subject-matter because it relates to the intra tracheal instillation of γ-interferon or TNF to rats rather than to their administration under the form of an aerosol as stated in claims 1 and 9. Yet the board is of the opinion that the intra tracheal instillation is sufficiently predictive of the effects of a gas suspension of particles introduced into the lung. This is because both ways of administration aim at the same purpose of bringing the drug into contact with the lung's alveoli. In view of the above findings, the board is satisfied that the patent in suit solves the problem as set out supra.

11. When assessing the inventive step in the light of the closest prior art, the relevant questions are (i) whether or not there was a pointer in the prior art which would have directed the skilled person to the solution adopted, namely that of specifically targetting the lung's alveoli and (ii) whether (s)he would have had a reasonable expectation of success in obtaining therapeutic levels of the drug in the bloodstream by applying this mode of drug administration. In the board's view, there was no such pointer, either in document (1), or elsewhere. Document (1) does not establish unambiguously that the **non-therapeutic** levels of insulin found in blood arrived there by intra pulmonary nebulization. Thus, it does not suggest at all that **therapeutic** levels of insulin can be obtained by intra pulmonary nebulization. Further, it is also worth remarking that the skilled person was at the priority date of the patent in suit at best uncertain as to whether a protein could enter the bloodstream from the lung (see document (18), page 356, last full paragraph: "...can represent a major barrier to the passage of larger molecules" and document (19), page 121, 1-h column, lines 5 to 6).

Therefore, there was also no reasonable expectation of success in obtaining therapeutic levels of the protein in the bloodstream by applying the mode of drug administration stated in claims 1 and 9.

12. In conclusion, the subject-matter of claims 1 and 9 and dependent claims 2 to 8 and 10 to 17 fulfils the requirements of Article 56 EPC. Since the board is satisfied that the claims of the main request meet the requirements of the EPC, there is no need to consider auxiliary requests B to L.

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 on the basis of the following documents:

   (a) Claims 1 to 17 submitted during oral proceedings as main request;

   (b) description: columns 1, 2, 4 to 6, 8 and 9, lines 1 to 16 of the patent as granted; and columns 3 and 7 filed on 18 November 1994.

The Registrar: The Chairwoman:

A. Townend U. M. Kinkeldey