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D E C I S I O N
of 19 April 2001

Case Number: T 0955/96 - 3.3.2

Application Number: 88908739.1

Publication Number: 0396549

IPC: A61K 9/50

Language of the proceedings: EN

Title of invention:
A drug composition with microspheres and process for its preparation

Patentee:
West Pharmaceutical Services Drug Delivery & Clinical Research Centre Limited

Opponent:
Teijin Limited

Headword:
Microspheres/WEST PHARMACEUTICAL SERVICES

Relevant legal provisions:
EPC Art. 54, 56, 83, 123
EPC R. 57a

Keyword:
"Sufficiency of disclosure: yes"
"Novelty: yes"
"Inventive step: no, obvious selection from the state of the art"

Decisions cited:
T 0020/81, T 0181/82, T 0197/86

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0955/96 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 19 April 2001

Appellant: (Opponent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 6 September 1996 concerning maintenance of European patent No. 0 396 549 in amended form.**

Composition of the Board:

Chairman: U. Oswald
Members: G. F. E. Rampold
H. Preglau

Summary of Facts and Submissions

I. The appellant originally filed notice of opposition to the grant of European patent No. 0 396 549 (European patent application No. 88 908 739.1) and requested that it be revoked in its entirety pursuant to Article 100(a) EPC on the grounds of lack of novelty and inventive step and also pursuant to Article 100(b) EPC because of insufficiency of disclosure. Claim 1 read as follows:

"A drug delivery composition which is suitable for transmucosal delivery and which comprises a plurality of microspheres adapted to gel in contact with the mucosal surface and active drug associated with each microsphere, the composition being free of an enhancer, characterized in that the drug is for systemic delivery and is a peptide having a maximum molecular weight of 6000 and in that the microspheres comprise starch, starch derivatives, gelatin, collagen, dextran or dextran derivatives but excluding DEAE dextran."

II. The following citations submitted in support of the opposition under Article 100(a) EPC remain relevant to the present appeal:

(1) L. Illum, "Microspheres as a Potential Controlled Release Nasal Drug Delivery System", published in Delivery Systems for Peptide Drugs, Plenum Press, New York and London, 1986, pages 205 to 210

(3) EP-A-0 122 036

(8) L. Illum, "Drug Delivery Systems for Nasal Application", published in Archiv For Pharmaci Og

Chemi, Vol. 94, No. 5, 1987, pages 127 to 135

III. The opposition division, in an interlocutory decision, maintained the patent in amended form in accordance with Article 102(3) EPC on the basis of the documents specified in the communication pursuant to Rule 58(4) EPC dated 6 September 1996. Claim 1 reads as follows:

"A drug delivery composition which is suitable for transmucosal delivery and which comprises a plurality of microspheres adapted to gel in contact with the mucosal surface and active drug associated with each microsphere, the composition being free of an enhancer, characterized in that the drug is for systemic delivery and is a peptide having a maximum molecular weight of 6000 and in that the microspheres comprise starch, starch derivatives, gelatin, collagen, or dextran."

Dependent claims 2 to 9 relate to specific elaborations of the composition according to claim 1.

Independent claims 10 and 11 relate to particular processes for preparing a composition as claimed in any one of claims 1 to 9.

IV. The opposition division argued in its decision in essence as follows:

In the absence of an adequate basis in the originally filed documents for the disclaimer "but excluding DEAE-dextran", claim 1 as granted contravened Article 123(2) EPC. The proprietor’s main request to reject the opposition and to maintain the patent unamended had accordingly to be refused.

As to the auxiliary request, the opposition division found that the opponent had failed to provide in its notice of opposition and during further prosecution of the case before the department of first instance any convincing facts, evidence or arguments relating to the ground of insufficiency of disclosure. Nor did the opposition division itself see any sound reason for calling into question the sufficiency of disclosure of the invention or for further pursuing this issue on its own motion under Article 114(1) EPC.

Concerning the grounds of opposition laid down in Article 100(a) EPC, the opposition division concluded that, contrary to the opponent's assertion, the subject-matter of the patent in suit was novel by comparison with the state of the art according to citation (3). More specifically, it held that, unlike the claimed formulations in the patent in suit consisting of regularly shaped and sized microspheres, the drug delivery systems for nasal application disclosed in citation (3) were powder compositions consisting of particles of irregular shape and size, and as such did not prejudice the novelty of the patent in suit.

As to inventive step, the opposition division considered that the teaching in the closest state of the art, which was in its opinion citation (8), suggested to those skilled in the art the use of microspheres for a controlled drug release system for nasal administration, which released the drug slowly.

In contrast to what the skilled person would have expected from the teaching in the closest state of the art, the specific choice of the appropriate material

from which to prepare the microspheres in combination with the delivery of peptides of a molecular weight less than 6000, as specified in claim 1 of the patent in suit, led unexpectedly, in the opposition division's opinion, to a rapid onset of action of nasally administered physiologically active polypeptides, such as calcitonin or insulin, and to a surprisingly sharp and fast bioavailability profile of the active drug. Since these favourable results were not predictable from the disclosure in (8), the opposition division considered the acknowledgment of an inventive step to be justified.

IV. The opponent and present appellant filed a notice of appeal against the decision of the opposition division and requested that the patent in suit be revoked in its entirety.

V. At the beginning of the oral proceedings before the board, held on 19 April 2001, the respondent substituted for its previously filed request, namely that the patent be maintained on the basis of the claims upheld by the opposition division, a modified request based on a revised set of claims 1 to 11 corresponding to those upheld by the opposition division (see paragraph III above), with the sole exception that in claim 1 collagen as one of the materials for the microspheres had been deleted.

VI. The appellant's arguments submitted in writing and during the oral proceedings can be summarised as follows:

In contrast to its objection as raised in the notice of opposition and upheld in the entire proceedings before

the opposition division and in the appeal statement as well, namely that the subject-matter in the patent in suit lacked novelty vis-à-vis the state of the art according to (3), the appellant confirmed at the begin of its submissions during the oral proceedings before the board that it did not wish to maintain lack of novelty as a ground for opposition.

As to the opposition on the ground of insufficiency of the disclosure, the appellant essentially argued that, according to the explicit disclosure in citation (3), the known powdery compositions were able to absorb moisture on the nasal mucous membrane upon their administration into the nasal cavity, thus making each particle, which was not in a viscous fluid state and did not flow away immediately but diffused moderately, stay at the site on the nasal mucosa. The clear implication of this disclosure was that the water-absorbing and water-insoluble base, used in (3) as the carrier material, formed gels in contact with the mucosal surface, as was required by the claims of the patent in suit. Should the board nevertheless follow the respondent’s conclusions submitted in writing that only formulations in the form of microspheres made from cross-linked starch had the capability of forming a gel in contact with the nasal mucosa, while powder formulations of cross-linked starch according to (3) did not, then the appellant intended to maintain its opposition under Article 100(b) EPC on the ground of insufficiency of the disclosure.

In the absence of any convincing evidence showing that microsphere formulations in accordance with the claimed invention, when used as drug delivery systems for nasal administration, were indeed superior to the powder

formulations disclosed in (3), the problem to be solved by the claimed invention could only be seen as that of providing some alternative formulations for nasal administration of physiologically active polypeptides.

Even if (3) did not expressly disclose microspheres, it was obvious and clearly lacking an inventive step to solve the above-indicated problem by simply substituting, for the microscopic substantially spherical particles of (3), microspheres containing the same base material. In accordance with the materials for the microspheres disclosed in the patent in suit, citation (3) taught, inter alia, the use of cross-linked starch and gelatin as suitable carrier materials. Before the priority date of the patent in suit both cross-linked starch (Spherex) and gelatin microspheres were publicly available. It was thus clear that the same materials were commercially available for use in both the powdery compositions of (3) and in the microsphere formulations according to the invention.

The use of microspheres was specifically taught in (8). This citation disclosed the results of experiments designed to investigate the efficacy of administering peptides via the nasal route and mentioned in this context particularly enkephalins, LHRH, calcitonin and insulin, all having molecular weights less than 6000 and all specifically described in the patent in suit.

Citation (8) taught that the use of absorption enhancers disturbed the integrity of the nasal membrane. The clear implication of this was that such enhancers should be avoided. Consequently, in order to avoid the use of enhancers, the author of (8) already suggested the use of an alternative strategy to

increase the absorption efficiency of drugs administered nasally by attempting to prevent the rapid clearance of the delivery system from the nose. This alternative strategy consisted in the development of a controlled release nasal drug delivery system in the form of microspheres made from materials that were known in the art to swell in contact with water to form a gel-like layer with good bioadhesive properties. The materials selected in (8) included, inter alia, starch.

What citation (8) therefore literally suggested to those skilled in the art was the idea that physiologically active polypeptides having a molecular weight below 6000, such as insulin or calcitonin, might advantageously be administered by the nasal route by delivering them in the form of microspheres of, for example, starch; and that this avoided the need for an absorption enhancer.

The conclusion, which formed in the impugned decision the basis for the acknowledgment of an inventive step, namely that the "selected microspheres" in combination with "selected drugs" led to a surprisingly sharp and fast bioavailability profile (pulsative release effect) not predictable from the teaching of (8), could not be justified. Thus, the "selected microspheres" and the "selected drugs" which produced the alleged pulsative release effect were respectively those of starch (microspheres) and insulin (drug). This was the only combination which was exemplified in the patent in suit and, accordingly, alleged by the respondent to show the claimed effect. There was, however, no justification for the opposition division to extrapolate this "specificity" or "selection" to all combinations embraced by the claims of the patent in suit.

Moreover, the "selected starch microspheres" were one of only three specifically mentioned in (8). Similarly the "selected drug", ie insulin, was one of eight specifically mentioned in citation (8), which in any case showed a particular interest in the administration of insulin. Furthermore it was difficult to accept that the general definition of the active drug in claim 1 as "a peptide having a maximum molecular weight of 6000" should be considered as a "selection" from a list of 8 specifically mentioned groups of peptides, all of which had a molecular weight in this range.

In conclusion, citation (8) clearly suggested to a person skilled in the art an absorption aid-free drug delivery composition for transmucosal delivery, which comprised microspheres of starch and peptides having a maximum molecular weight of 6000. As the author of citation (8), in the context of a reference to the powder formulations of (3), already reached the express conclusion that the microsphere systems should provide similar or even better effects, she led those skilled in the art to expect that such microsphere compositions should provide desirable and favourable results, when used as drug delivery systems for the nasal administration of physiologically active polypeptides.

VII. The respondent disagreed, essentially relying on the following arguments:

Neither the appellant nor the opposition division in its decision thought, that citation (3) was particularly relevant to the assessment of inventive step, even though it had been the main document considered in relation to novelty. With regard to

inventive step, although the complete disclosure of (3) could not be ignored, it was appropriate to concentrate on the specific, worked examples in (3) and the intention behind this citation. In (3) the specific examples were all concerned with microcrystalline cellulose. This material was structurally quite distinct from the microspheres of the present invention and functionally quite different as well, in that this material did not gel in contact with the mucosal surface.

Although the purpose of citation (3) might be similar to that of the present invention, namely to deliver drugs efficiently through the nasal mucosa, the means in (3) were quite different from those to which the patent in suit was limited, and the effect of choosing those different means was also different.

The intention in (3) was simply to make sure that the drug-containing composition remained in place on the nasal mucosa, to allow the drug to be absorbed before the drug was physically lost from the nose. Simple retention of the drug-containing formulation in the nose had, however, merely the effect of a prolonged release of the drug.

The gelling microspheres of the present invention led to a different release profile, namely a very rapid release shortly after administration. This beneficial effect had been clearly shown by the figures set out in the patent itself and, moreover, by the experimental results reported in the declarations from the inventor. From these experimental results it could be seen that the effect of administering the gelling microspheres containing insulin was surprisingly very similar to the

effect of injecting insulin. The results obtained were very surprising and could not have been predicted from an understanding of the action of the microspheres at the priority date of the invention.

In summary, (3) did not disclose the same materials as the present invention, the materials that were disclosed in (3) did not achieve the same effect, and the effect achieved was not suggested even as being desirable in (3).

The respondent was prepared to accept that citation (8) was more relevant than (3), since it already disclosed microsphere compositions. However, this aspect in (8) had to be seen in the context of the technical teaching of the whole Article and the impact that it actually had at the priority date of the contested patent for a skilled practitioner in the art concerned with the claimed invention.

Although the teaching of (8) related principally to the delivery of peptides and proteins, it was not exclusively concerned with these types of drug. There was certainly no emphasis on the peptides having a molecular weight of below 6000, as was a requirement in the present invention. The list of desirable properties for a nasal controlled release system, as set out in Table 3 of (8), were simply the same sort of aims with which (3) was already concerned, namely that the formulation should be cleared slowly from the nose and should release the drug slowly.

The three microsphere systems chosen in (8) were those based on albumin, starch-Spherex and DEAE-dextran. The declaration from the inventor demonstrated clearly that

microspheres based on albumin and DEAE-dextran did not provide the very large and fast decrease in plasma glucose level which could surprisingly be achieved when insulin was administered with microspheres made from the materials in accordance with the present invention. The experiments reported in (8) were strictly preliminary ones and the main paragraph on page 132 was at least equivocal about whether or not the use of absorption enhancers such as bile salts was desirable or even necessary for the microsphere systems disclosed in (8).

The experiments reported in (8) solely concerned preliminary investigations on the clearance of microsphere formulations from the nose in the absence of an active drug, but did not include any results concerning the effects, for example on blood glucose level, resulting from the administration of an active drug, such as insulin, associated with microspheres.

Hence, there was no reason for the skilled reader at the priority date to expect that the microsphere drug delivery systems based on certain specific materials proposed in (8) were actually going to be any better than powder formulations disclosed in the prior art.

Certainly, there was no suggestion that, by choosing the appropriate material from which to prepare the microspheres, and by delivering drugs of a molecular weight less than 6000, the very specific release characteristics demonstrated in the patent in suit and in the inventor’s declarations could be obtained.

VIII. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the appeal be dismissed and that the patent be maintained on the basis of the set of claims presented during the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. In support of the proposed amendment concerning the deletion of collagen as one of the materials for the microspheres specified in claim 1, the respondent submitted during the oral proceedings that, in contrast to the situation with the other materials used for the microspheres defined in claim 1, no comparative data were available in the file demonstrating the superiority of collagen microspheres over other sorts of microspheres suggested as drug delivery systems in the state of the art according to (1) and (8), namely DEAE-Sephadex or HSA (human serum albumin) microspheres.

Consequently, the restrictive amendment offered by the respondent can fairly be said to constitute a bona fide attempt at overcoming certain objections to the claimed subject-matter in the patent in suit on the ground of lack of inventive step, which would constitute a ground for opposition specified in Article 100 (a) EPC. It is therefore deemed admissible under the terms of Rule 57a EPC.

Moreover, since the amendment to the respondent's current request was immediately recognisable as an

acceptable limitation of the scope of claim 1, the board decided to admit this request into the proceedings for consideration, in spite of its late filing.

3. The current wording of the claims does not give rise to any objections under Articles 84 and 123(2) or (3) EPC. Since this has not been disputed by the appellant, there is no need to expand in detail on this matter.

4. None of the documents available in the present proceedings and citable under Article 54(2) EPC discloses a drug delivery composition comprising microspheres associated with a peptide having a maximum molecular weight of 6000 as the active drug. Consequently, as regards the novelty of the claims under consideration in this appeal, the board has no reason to differ from the reasoning and the conclusion of the opposition division and does not consider further discussion of this issue to be appropriate, since it is apparent from paragraph VI above that the novelty of the claimed subject-matter in the patent in suit was no longer contested by the appellant during the oral proceedings before the board.

5. According to the established jurisprudence of the Boards of Appeal (see "Case Law of the Boards of Appeal of the European Patent Office", 3rd edition 1998, D. 3.1, pages 111 ff), the closest prior art for the purpose of objectively assessing inventive step is generally that which corresponds to an identical or similar use to that described in the claimed invention and, at the same time, requires the minimum of structural and functional modifications to arrive at the claimed subject-matter.

5.1 Both citations (1) and (8) discuss certain experiments designed to create and investigate suitable options for the nasal administration of peptides and proteins. These citations refer in this context, inter alia, broadly to investigations in which microsphere systems made from various materials were administered to the nasal cavity in the absence of any active drug to study the retention time of these microspheres on the nasal mucosa and their clearance properties from the nose, as compared with powders of the same materials and solutions. However, administration of microspheres with an active drug or their use in a complete drug delivery system is disclosed in neither (1) nor (8).

5.2 On the other hand, citation (3) discloses complete drug delivery systems in the form of powdery compositions for nasal administration of physiologically active polypeptides. The compositions described in (3) are free of an enhancer and comprise a physiologically active polypeptide or its derivative as the active drug, such as calcitonin or insulin, associated with a powdery water-absorbing and water-insoluble carrier, to allow said polypeptide, when nasally administered, to be effectively absorbed through the nasal mucosa. Thus, citation (3) already discloses drug delivery systems for the effective nasal administration of peptides having a molecular weight in the range specified in present claim 1.

Moreover, the overall aim of citation (3) is the same as, or at least similar to, the aim of the claimed invention, namely to effectively deliver certain peptides, such as insulin, through the nasal mucosa. Consequently, on the basis of the principles set forth above, the disclosure of (3) comes undoubtedly closer

to the claimed subject-matter in the patent in suit than that of (1) or (8).

5.3 In the drug delivery system of (3), at least 90 per cent by weight of the particles of the powdery composition have an effective diameter in the range of 10 to 250 microns (see page 9, lines 22 to 24), which actually includes the range of 10 to 100 microns given for the diameter of the microspheres specified in the patent in suit (see column 3, lines 25 to 26). The water-absorbing and water-insoluble carrier is selected, for instance, from diverse sorts of cellulose materials, eg cellulose as such, crystalline cellulose, sodium carboxymethyl cellulose; but also from water-absorbing and water-insoluble starches such as hydroxypropyl starch, carboxymethyl starch, cross-linked starch; water-absorbing and water-insoluble proteins such as gelatin, casein; water-absorbing and water-insoluble gums such as gum arabic, tragacanth gum; and cross-linked vinylpolymers such as cross-linked polyvinyl pyrrolidone, cross-linked polyvinyl alcohol and polyhydroxyethylmethylmethacrylate (see page 7, lines 22 to 35).

As is the case with the drug delivery systems according to the claimed invention, the powdery compositions forming the drug delivery systems in (3) may have different structures, for example one in which the water-absorbing and water-insoluble carrier and the polypeptide form independent particles, one in which the polypeptide particles adhere to the surface of the water-absorbing and water-insoluble carrier, one in which the polypeptide particles are dispersed in the water-absorbing and water-insoluble carrier particles, forming separate phases of their own, or one in which

the polypeptide particles are closely dispered in the water-absorbing and water-insoluble carrier, thus forming a uniform dispersion (see (3), page 10, lines 13 to 26).

5.4 As is demonstrated in Examples 2, 4 and 6 (see also especially Table 1 on page 19) and can clearly be derived from Figures 1 and 2, the drug delivery systems disclosed in (3) show in animal experiments a high and efficient absorption of nasally administered insulin or calcitonin, with a rapid onset of action of the drug after administration. When, for example, insulin is used as the physiologically active polypeptide, the data reported in (3) demonstrate a favourably sharp bioavailability profile with fast and significant decrease of the plasma glucose concentration (see especially Figure 1) on the one hand, and a fast and significant increase of the serum insulin level, on the other (see especially Figure 2), depending on the particular material used for the powder formulations disclosed in (3).

5.5 Notwithstanding the above, in its written submissions and during the oral proceedings the respondent essentially relied in support of inventive step on the allegation that bioadhesive microsphere systems according to the claimed invention, when administered nasally, were capable of enhancing greatly the bioavailability of polar drugs as compared with the powder formulations disclosed in (3). Furthermore, the respondent argued that intranasal administration of the claimed drug delivery systems - as demonstrated in the patent in suit and in the inventor's declarations by formulations comprising insulin as the active drug associated with microspheres made from starch, cross-

linked starch, gelatin, or dextran - resulted in animal tests (sheep) in a significantly better absorption of insulin through the nasal mucosa, a more rapid onset of the effect of the active drug administered and, consequently, in an improved bioavailability profile of insulin with a significantly increased reduction in the plasma glucose level, as compared with the administration of powder formulations of insulin disclosed in the closest state of the art according to (3).

5.6 These alleged advantages are said to be proved by the results of the comparative tests submitted in the two declarations by Professor Illum, who is named as the inventor of the patent in suit. The first Illum declaration was originally filed on 9 June 1992 during the examination proceedings (hereinafter referred to as the "first declaration") for the particular purpose of demonstrating the superiority of a first group of lyophilised drug delivery systems containing insulin as the active drug associated with microspheres according to the invention made from cross-linked starch, gelatin or Sephadex (dextran) over a second group including HSA or DEAE-dextran microspheres outside of the present claims.

The results shown for the first group, ie cross-linked starch, gelatin and Sephadex (dextran) microspheres with insulin as the active drug reported in the "first declaration", were used in the present appeal for comparison with the results reported in the second Illum Declaration, which was filed with the respondent's letter dated 17 May 1996 during the first-instance opposition proceedings and which purports to study the intranasal absorption of insulin from a

lyophilised powder formulation in accordance with the disclosure in (3) (hereinafter referred to as the "second declaration"). In both declarations, insulin absorption was assessed indirectly by measuring plasma glucose concentrations.

5.7 However, to be relevant, such comparative tests must meet certain criteria. These include in the present case the choice of a microsphere formulation according to the claimed invention and of a comparative powder formulation taken from the closest state of the art; at the same time, the pair being compared should possess maximum similarity with regard to the materials and the drugs used, the structure and the application (see decision T 181/82, OJ EPO, 1984, 401). Moreover, the nature of the comparison with the closest state of the art should be such that any alleged advantages or beneficial effects are convincingly shown to have their origin in the distinguishing feature of the invention vis-à-vis the closest state of the art (see decision T 197/86, OJ EPO, 1989, 371).

5.8 Contrary to the respondent's submissions, the comparative tests presented in the present case are not pertinent, since the criteria set forth above have not been met for a number of reasons, including in particular the following:

Firstly, microsphere formulations according to the invention made from cross-linked starch or gelatin, as described in the "first declaration", were not compared with powder formulations according to (3) made from the same materials, ie cross-linked starch or gelatin, as might have been expected, but with powder formulations made from a structurally entirely different material,

namely microcrystalline cellulose, although at least starch, cross-linked starch and gelatin are explicitly disclosed as particularly suitable materials both for the microsphere formulations in the contested patent (see column 3, lines 29 to 31) and likewise for the powder formulations in (3) (see page 7, lines 25 to 27; 29). According to the respondent's own submissions, microcrystalline cellulose is structurally quite distinct from the materials used for the microspheres of the present invention and is functionally quite different as well, in that it does not gel in contact with the mucosal surface.

Secondly, whereas in the tests recorded in the "first declaration" semi-synthetic human Na-insulin was used as the active drug to produce a stock Na-insulin solution with a concentration of 96 IU/ml (3.45 mg/ml) for the preparation of the lyophilised insulin microsphere formulations according to the claimed invention, human zinc insulin was used to produce a zinc insulin stock solution with a concentration of 66.67 IU/ml (2.598 mg/ml) for the preparation of the lyophilised insulin powder formulation according to the state of the art of (3).

The board cannot accept the respondent's argument submitted during oral proceedings that in the "second declaration" zinc insulin was transformed into Na-insulin prior to its use for the preparation of a powdery drug delivery system according to (3), and that accordingly the particular form of the insulin used was in both cases the same. First of all, in the "second declaration" it is clearly indicated under the heading "Loading the administration devices" that "the total theoretical weight of material in the formulation was

623.38 mg comprising 600 IU (23.38 mg) zinc insulin and 600 mg crystalline cellulose;" and further down on the same page under the heading" Measurement of insulin content by HPLC" that "the zinc insulin content of the formulation was determined by HLPC analysis". The fact that, contrary to the respondent's claim the form of the insulin used in the "second declaration" was necessarily different from that used in the "first declaration" is moreover entirely clear from the circumstance that in the "first declaration" a dose weight of 2.0 IU insulin/kg corresponds to 0.071 mg/kg of the particular form of insulin used (see Table 2), while in the "second declaration" a dose of 2.0 IU insulin/kg corresponds to 0.078 mg/kg of an apparently different form of insulin used (see "Loading the administration devices", paragraph 2, line 3).

Thirdly, although the attention of the skilled reader is drawn in (3) (see especially page 9, line 22 to page 10, line 12), as in the patent in suit (see especially column 3, lines 24 to 26), to the particular importance of the particle size of the drug delivery system in nasal deposition and in the effective absorption of the active drug from the nasal mucous membrane, no data are available in the respondent's comparative experiments as to the specific values and the distribution of the particle size either for the powdery composition disclosed in (3) or for the microspheres according to the claimed invention. In the absence of such data, the results given in the comparative experiments are therefore, for this reason too, not exactly comparable.

5.9 The board accepts the respondent's submission that microcrystalline cellulose is referred to in citation

(3) as an especially desirable carrier material for the known powdery drug delivery systems (see page 8, lines 2 to 3) and is used as the carrier material in the majority of the examples contained in (3). However, if the respondent regards only the preferred powder formulations from citation (3) as comparable, it is concentrating on the technical progress compared with the most effective formulations disclosed in the state of the art according to (3). But technical progress is not a requirement for a patent under the EPC.

5.10 According to the established case law of the boards of appeal (see "Case Law of the Boards of Appeal of the European Patent Office", 3rd edition 1998, D. 7.7.2, pages 144-145), some beneficial effects or advantageous properties, if appropriately demonstrated by means of exactly comparable results, could in certain circumstances properly form a basis for the definition of the problem the claimed invention sets out to solve and could, in principle, be regarded as an indication of inventive step; the only comparative tests suitable for this are, however, those which are concerned with the structurally closest state of the art to the invention, because it is only here that the factor of unexpectedness is to be sought (see decision T 181/82, loc. cit.). As is entirely clear from the observations in point 5.8 above, these requirements are not met in the present case.

5.11 Consequently, the conclusion must be drawn that the additional advantages referred to by the respondent have not been properly demonstrated. Such alleged but unsupported advantages cannot be taken into consideration for the purpose of determining the problem the invention sets out to solve, or, therefore,

in the assessment of inventive step (see decision T 20/81, OJ EPO 1982, 217).

5.12 For this reason, the problem to be solved by the claimed invention vis-à-vis the closest state of the art may only be seen as that of providing an alternative drug delivery system for transmucosal administration of physiologically active polypeptides.

The solution to the problem was the provision of the drug delivery composition according to claim 1, wherein microspheres comprising starch, starch derivatives, gelatin or dextran associated with an active drug were substituted for powder formulations of the same material used for the drug delivery system disclosed in (3). On the basis of the experimental data provided in the examples in the patent in suit (see especially Examples 1 and 2; Figure 1 to 7) and in the "first declaration" as well, and, moreover, in the absence of any evidence to the contrary, the board is satisfied the problem has been plausibly solved. Since this was not contested, it is not necessary to go into further detail on this point.

6. It still remains to be determined whether the requirement of inventive step is met by the claimed subject-matter.

6.1 The skilled practitioner seeking a solution to this problem in the state of the art was undoubtedly aware of the prior art of citations (1) and (8). The author of both these citations refers in them to powder formulations as disclosed in (3) and points the person skilled in the art clearly and unequivocally in the direction of microsphere formulations for nasal

administration of physiologically active polypeptides as a particularly suitable and even potentially advantageous alternative to the known powder formulations, by stating:

"We believe that our microsphere systems should provide similar or even better effects [as compared to powder formulations]; their physical properties should also allow for better administration and deposition behaviour since it is possible to prepare such systems in a variety of sizes" (see (1): end of page 209).

Similarly, in the first full text paragraph on page 134, the author of (8), who is the present inventor and incidentally also the author of (1), starts with a reference to various powder formulations for nasal application of active drugs, including insulin, and concludes at the end of this paragraph: "we believe that our microsphere systems should provide similar or even better effects."

6.2 However, citations (1) and (8) both not only provide the skilled reader with a merely abstract and general suggestion that microsphere systems might be a particularly favourable or even superior alternative to powder formulations for the nasal administration of peptides, but the skilled person is also given precise instructions - should he really need them - as to (i) the appropriate materials for preparing microspheres which will ensure a high and efficient absorption of the active drug through the nasal mucosa, (ii) the appropriate size distribution of such microspheres to enhance the bioavailability of the drug administered and (iii) the kind of active drugs to be favourably associated with the microspheres to arrive at a

complete and effective drug delivery system for nasally administering physiologically active polypeptides.

6.3 During the oral proceedings before the board, a lengthy discussion focused on the question whether or not the state of the art according to (3) already suggested the use of powder formulations which are capable of forming a gel-like layer in contact with nasal mucosa, or whether the respondent was correct in stating that the teaching of (3) would dissuade those skilled in the art, faced with the stated technical problem, from using microspheres which are adapted so as to gel in contact with the mucosal surface, as required by the present claims.

However, any further discussion on this question is superfluous, since citation (8) (see especially page 133, first paragraph, lines 8 to 10, Table 4) already clearly and unequivocally suggests solving the problem by choosing "microspheres made from materials that are known to swell in contact with water to form a gel-like layer with good bioadhesive properties" and recommends in this context, *inter alia*, cross-linked starch (starch Spherex) as a suitable gelling material, which is likewise used as a suitable material for the microspheres according to the claimed invention (see claim 1) and also the powder formulations disclosed in (3) (see especially page 7, line 27).

In the context of microsphere delivery systems for nasal administration of peptides, the teaching of citation (1) (see especially end of page 206) makes it likewise clear to a person skilled in the art that "an important requirement for bioadhesive polymer materials is their ability to swell by absorbing water from the

mucous layer in the nasal cavity thereby forming a gel like structure in which environment the interpenetration of polymer and glycoprotein chains can take place and the bondings can form rapidly".

6.4 In view of the foregoing observations, the board is unable to accept any of the respondent's repeated assertions, namely (i) that (3) did not disclose at least partly the same materials as used in the claimed invention, (ii) that such materials did not achieve the same effect of gelling when used for the powder formulations disclosed in (3), and that the effect of gelling in contact with nasal mucosa was not even suggested in (3) as being desirable.

Apart from the fact that the respondent was unable to give a technically acceptable explanation in support of its assertion that microsphere formulations made from cross-linked starch, as opposed to powder formulations of such starch, gel in contact with the nasal mucosa, the above-mentioned reference in (8) makes it quite clear that, in sharp contrast to what the respondent sought to suggest, it is indeed the specific choice of the material which is responsible for the capability of a given formulation or composition to form a gel in contact with the nasal mucous, rather than the particular formulation as such of that material as powders or microspheres.

6.5 Citation (8) already recommends the use of microspheres having a diameter of the order of 40 to 60 microns (see page 133, end of the first paragraph), which corresponds exactly to the preferred diameter of the microspheres used for the claimed drug delivery system in the patent in suit (see column 3, line 26).

6.5 Accordingly, the use of microspheres which are adapted so as to gel in contact with the mucosal surface and which have a diameter in the order of 40 to 60 microns, was patently obvious to a person skilled in the art, faced with the stated problem and familiar with the state of the art according to (1) or (8), and can evidently contribute nothing to the inventive step of the proposed solution.

6.6 In line with the conclusions of the opposition division in the impugned decision, the respondent argued during the oral proceedings before the board that it would be justified to acknowledge an inventive step, since the allegedly superior and improved release characteristics of the claimed drug delivery system were the result of choosing the appropriate material from which to prepare the microspheres and of delivering peptides having a maximum molecular wight of 6000. The board cannot agree in essence for the following reasons:

Cross-linked starch is already suggested in (1) and (8) as a particularly suitable material for microspheres which are intended to be used in the nasal administration of peptides. Its choice as a material for the microspheres of the drug delivery system according to the claimed invention was therefore patently obvious to a person skilled in the art. As explained in great detail in points 5.5 to 5.12 above, the allegedly superior and improved release characteristics of the claimed drug delivery system in comparison with the closest state of the art have never been adequately demonstrated.

In this respect it should also be noted that, contrary to what the respondent sought to suggest and what was

apparently accepted by the opposition division, the test results presented in the "first declaration" are not pertinent at all to the assessment of inventive step of the claimed invention. In the present case, cross-linked starch, which was already used for the microspheres disclosed in the prior art of (1) and (8), suggested itself to a person skilled in the art, for the reasons stated above, as a particularly suitable material for the microspheres of the claimed drug delivery system. In the absence of any evidence showing that **the obvious choice of this particular material** from the limited number of three options (albumin, starch-Spherex, DEAE-Sephadex) disclosed in (1) and (8) was unexpectedly associated with a significant improvement or advantage in comparison with the closest state of the art, the acknowledgment of an inventive step cannot be based on the results of certain comparative tests demonstrating that the cited documents (1) and (8) also disclose some other materials for microspheres which possibly exhibit less advantageous properties in certain tests than the one actually taken in an obvious manner from the cited state of the art, as is the case with the comparative experiments presented in the "first declaration". To acknowledge an inventive step on the basis of such comparative tests would be to fundamentally misunderstand the well established criteria in the jurisprudence of the EPO for determining whether or not a selection from the state of the art is inventive for patent purposes.

Finally, apart from the fact that virtually all the examples of peptides mentioned in Table 1 on page 129 of (8) as desirable for nasal absorption have a molecular weight of less than 6000 and, accordingly,

render obvious the selection of this particular class of peptides as the active drugs associated with the microspheres of the claimed invention, no evidence has been provided to show that microspheres associated with peptides having a maximum molecular weight of 6000 would entail any unexpected advantages over microspheres associated with peptides having a molecular weight greater than 6000.

6.7 For all these reasons, the board concludes that the claimed subject-matter in the patent in suit results from an obvious combination of the teaching of citation (3) with that of (1) or (8) and is therefore devoid of inventive step contrary to the requirements of Article 52(1) in conjunction with Article 56 EPC.

7. The opposition under Article 100(b) EPC on the grounds of insufficiency (Article 83 EPC), as maintained by the appellant during the oral proceedings before the board (see paragraph VI above), has already been dealt with in points 6.3 and 6.4 above in the context of the board's observations as to the capability of cross-linked starch to gel in contact with the nasal mucous layer. Since, moreover, the patent has to be revoked in any case for other reasons, insufficiency as a ground for opposition is no longer of relevance to the present case.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman

A. Townend U. Oswald