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**Datasheet for the decision
of 14 December 2009**

Case Number: T 0997/06 - 3.3.04

Application Number: 97928123.5

Publication Number: 0921812

IPC: A61K 38/28

Language of the proceedings: EN

Title of invention:

Insulin preparations containing a halogenide

Patentee:

NOVO NORDISK A/S

Opponent:

Sanofi-Aventis Deutschland GmbH

Headword:

Insulin Preparation/NOVO NORDISK

Relevant legal provisions:

EPC Art. 56, 84, 123(2)

Relevant legal provisions (EPC 1973):

-

Keyword:

"Main request: added matter (no), clarity (yes), inventive step (no)"

"First auxiliary request: added matter (no), inventive step and sufficiency of disclosure (yes)"

Decisions cited:

T 0425/98, T 0457/98

Catchword:

-



Case Number: T 0997/06 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 14 December 2009

Appellant:
(Patent Proprietor)

NOVO NORDISK A/S
Novo Allé
DK-2880 Bagsvaerd (DK)

Representative:

Hoffmann Eitle
Patent- und Rechtsanwälte
Arabellastraße 4
D-81925 München (DE)

Respondent:
(Opponent)

Sanofi-Aventis Deutschland GmbH
Patent- und Lizenzabteilung
Industriepark Höchst
Geb. K 801
D-65926 Frankfurt am Main (DE)

Representative:

Weiss, Wolfgang
Weickmann & Weickmann
Patentanwälte
Kopernikusstrasse 9
D-81679 München (DE)

Decision under appeal:

**Decision of the Opposition Division of the
European Patent Office posted 7 June 2006
revoking European patent No. 0921812 pursuant
to Article 102(1) EPC 1973.**

Composition of the Board:

Chairman: U. Kinkeldey
Members: B. Claes
F. Blumer

Summary of Facts and Submissions

I. The appellant (proprietor) lodged an appeal against the decision of the opposition division revoking European patent No. 0 921 812 which was granted for European patent application No. 97928123.5 which had been published as WO97/48414.

Claim 1, 4, 5 and 14 to 18 of the application as published read:

"1. An aqueous insulin preparation comprising:
human insulin, an analogue thereof and/or a derivative thereof,
glycerol and/or mannitol, and
5 to 100 mM of a halogenide.

4. An insulin preparation according to any of the preceding claims, comprising an analogue of human insulin wherein position B28 is Asp, Lys, Leu, Val or Ala and position B29 is Lys or Pro; or des(B28-B30), des(B27) or des(B30) human insulin.

5. An insulin preparation according to claim 4, comprising an analogue of human insulin wherein position B28 is Asp or Lys, and position B29 is Lys or Pro, preferably Asp^{B28} human insulin or Lys^{B28}Pro^{B29} human insulin.

14. An insulin preparation according to any of the preceding claims, comprising:
10 to 40 µg Zn/100 U insulin, preferably 10 to 26 µg Zn/100 U insulin.

15. An insulin preparation according to any of the preceding claims, comprising:
0 to 5 mg/ml, preferably 0 to 4 mg/ml, of a phenolic compound.
16. An insulin preparation according to claim 15, comprising:
0.5 to 4.0 mg/ml, preferably 0.6 to 4.0 mg/ml, of m-cresol and 0.5 to 4.0 mg/ml, preferably 1.4 to 4.0 mg/ml, of phenol, or a mixture thereof.
17. A parenteral pharmaceutical formulation comprising an insulin preparation according to any of the preceding claims.
18. A method for improving the chemical stability of an insulin preparation comprising human insulin or an analogue or a derivative thereof, which method comprises adding glycerol and/or mannitol and 5 to 100 mM of a halogenide to said preparation."
- II. Claims 1, 4, 5 and 15 to 18 of the granted patent were identical to the same claims in the application as published.
- III. The patent had been opposed on the grounds for opposition under Article 100(a) EPC, in combination with Article 54 EPC (novelty) and Article 56 EPC (inventive step), and Article 100(b) EPC. The opposition division revoked the patent because claim 1 of the main and auxiliary request before them lacked inventive step.

- IV. With the statement of the grounds of appeal the appellant filed a new main request and five auxiliary requests, a new document, test data dated 9 October 2006 and two test reports dated 18 September 2006.
- V. The respondent filed submissions in answer to the appellant's grounds of appeal on 4 May 2007.
- VI. The appellant filed further observations and a new main request and five auxiliary requests replacing the previous requests on file and a supplementary test report dated 29 January 2008. Further observations and a second supplementary test report dated 8 September 2009 were filed by the appellant after the respondent had filed observations in answer to appellant's submissions on 22 April 2008. The final submissions were filed by the respondent on 13 November 2009.
- VII. Oral proceedings took place on 14 December 2009. During these oral proceedings the appellant filed a new main request and two auxiliary requests.

Independent claim 1 of the main request read:

"1. A parenteral pharmaceutical formulation comprising an aqueous insulin preparation comprising:
Asp^{B28} human insulin,
glycerol and/or mannitol,
5 to 100 mM of a halogenide,
a mixture of 0.5 to 4.0 mg/ml, preferably 0.6 to 4.0 mg/ml, of m-cresol and 0.5 to 4.0 mg/ml, preferably 1.4 to 4.0 mg/ml of phenol as phenolic compounds, wherein the content of phenolic compounds is not more than 5 mg/ml,

10 to 40 µg Zn/100 U insulin, preferably 10 to 26 µg Zn/100 U insulin, and a phosphate buffer." (emphasis added by the board)

Claims 2 to 5 were dependent claims defining further embodiments of the subject-matter of claim 1.

Claims 1 to 5 of the first auxiliary request were identical to claims 1 to 5 of the main request but for the wording "1. A parenteral pharmaceutical formulation consisting of an aqueous insulin preparation consisting of: ..." (emphasis added by the board) in claim 1, i.e. a change of the "comprising" wording to the "consisting of" wording.

VIII. The following documents are referred to in this decision:

(D1): US 4,472,385

(D3): US 4,783,441

(D4): Brange & Lankjær (1992). Acta Pharm. Nord., Vol. 4, Nr. 3, p. 149-158.

(D6): EP-A-0 375 437

(D8): Wallhäußer (1995), Praxis der Sterilisation Desinfektion - Konservierung, p. 425-426.

(D9): Whittingham *et al.* (1998), Biochemistry, Vol. 37, p. 11516-11523.

(D11): "Galenics of Insulin", Jens Brange, Springer Verlag, 1987.

(D12): Brems *et al.* (1992), Protein Engineering, Vol. 5, No. 6, p. 527-533.

IX. The appellant's arguments, relevant for the present decision, can be summarised as follows:

Main request - Claim 1

Amendments - Article 123(2) EPC

- Claim 1 was based on a combination of claims 1, 5 and 14 to 17 of the published application with further support for the phosphate buffer on page 6, lines 1 to 3 of the published application and additional support for the mixture of cresol and phenol on page 5, lines 18 to 25, of the specification as published.

- There was no requirement in the amended independent claims 1 to specify the amount of insulin comprised. The sentence starting at page 5, line 18, ended on line 22 with a full stop. The specification of the amount of a phenolic compound, referred to in line 23 to 25, was therefore a "stand alone" disclosure which was not restricted to the amount of insulin in the formulation.

Inventive step - Article 56 EPC

- Document (D1) represented the closest prior art. The problem to be solved was the provision of a

parenteral pharmaceutical insulin formulation having improved chemical stability while the physical stability was not deteriorated.

- The subject-matter of claim 1 differed from the formulation in example 9 in document (D3) in three aspects, namely that a surface active substance (i.e. a detergent, namely linear polypropylene glycol) was used, in that a bovine insulin was used and that no m-cresol was present.
- The choice of human Asp^{B28} insulin for parenteral insulin preparations was not obvious in the light of document (D6) which disclosed, as preferable insulin analogues with a low ability to associate, rather human insulin analogues with a positively charged amino acid at the B28 position, than AspB28.
- The passage in document (D8) on page 425, left hand column, lines 38 to 48, where it was stated that newly registered human insulin preparations contained powerful phenol derivatives (addition of 0,06% Phenol and 0,15-0,25% m-cresol), which had already at an early time been applied as anti-bacterial agents, would not be interpreted by the skilled person as suggesting mixtures of phenol and m-cresol for use in insulin preparation.
- Post-published document (D9) disclosed that the Asp^{B28} insulin analogue was a monomeric, rapid-acting hormone for therapeutic purposes having a mutation at the dimer-forming surface of the insulin monomer. The mutation was effective in

destabilising the insulin dimer, giving rise to an essentially monomeric insulin at physiological concentrations. The document thus confirmed that that the Zn-complexed Asp^{B28} human insulin in combination with phenol and m-cresol provided a rapid-acting preparation. As far as stability was concerned phenol was the preferred additive. However, considering the requirements for a satisfactory preservation, its sole use did not provide a sufficient effect. Hence it had been found that a combination of phenol and m-cresol gave a satisfactory result for preservation of the Zn-complexed Asp^{B28} human insulin.

First auxiliary request

Amendments - Article 123(2) EPC

- The amendment of claim 1 changing the wording from "comprising" to "consisting of" did not constitute added matter.
- Moreover, examples II to IV of the application as published fell within the ambit of claim 1.

Inventive step - Article 56 EPC

- Document (D1) represented the closest prior art. The problem to be solved was the provision of a parenteral pharmaceutical insulin formulation having improved chemical stability while the physical stability was not deteriorated.

- Document (D1) disclosed in column 3, lines 35 to 40, that "*the presence of calcium or magnesium precipitating or complexing anions, such as phosphate ..., is avoided in the insulin solutions of this invention.*" This statement rendered the subject-matter of claim 1, which required the presence of phosphate buffer, inventive.
- X. The respondent's arguments, relevant for the present decision, can be summarised as follows:

Main request - Claim 1

Amendments - Article 123(2) EPC

- The preferred embodiment on page 5, lines 18 to 25, of the application as published required the insulin formulation as amended to comprise the specific amount of 60 to 3000 mmol/ml of human insulin or insulin analogue or derivative. The same preferred embodiment on page 5 lacked any reference to Asp^{B28} human insulin. Due to the lack of these specific features in the wording of the independent claims, these claims did not meet the requirements of Article 123(2) EPC.
- Claim 15 as originally filed and the passage on page 5, line 22, referred merely to "0 to 5 mg/ml, ..., of **a** phenolic compound". The upper range of 5 mg/ml could therefore not support the upper limit of a total content of a mixture of more than one phenolic compounds (i.e. m-cresol and phenol). The originally disclosed range was

not disclosed in linear combination with a mixture of phenolic compounds.

- The only reference to a method for improving the chemical stability of an insulin preparation in the specification as published was on page 6, lines 6 to 9. This passage lacked however any reference to features relating to phenol/cresol, a phosphate buffer and an amount of Zn.
- Furthermore, the passage on page 3, lines 18 to 20, of the application as published lacked any reference to a superior chemical stability of an insulin preparation and the presence of a phosphate buffer. Claim 6 lacked therefore compliance with Article 123(2) EPC.

Clarity - Article 84 EPC

- Claim 15 as originally filed and the passage on page 5, line 22, referred merely to "0 to 5 mg/ml, ..., of a phenolic compound". The upper range of 5 mg/ml in the amended claims 1 and 6 was therefore unclear as it referred to a total content of a mixture of more than one phenolic compounds (i.e. m-cresol and phenol).

Inventive step - Article 56 EPC

- Either of documents (D1), (D3) or (D12) represented the closest prior art.
- AspB28 human insulin was known in the art *inter alia* from document (D12).

- Both document (D11) and document (D8) disclosed the combined use of phenol and m-cresol as preservatives for insulin preparations.

First auxiliary request

Amendments - Article 123(2) EPC

- The amendment of "comprising" to "consisting of" resulted in a new combination of features in the claim which had not been disclosed in the application as filed.

Inventive step - Article 56 EPC

- Document (D1) represented the closest prior art.
- It could be taken from paragraph [0028] of the patent in suit that the inventors did not see the choice of the phosphate buffer as the core of the invention.
- Document (D4) disclosed that phosphate was a suitable buffer for pharmaceutical insulin preparations (see page 150, left-hand column, lines 1 to 7 of the section "Results and discussion" and page 152, right hand column, section "effect of buffer").

Sufficiency of disclosure

- From Figure 4 in document (D4) it was clear that the formation of covalent dimer and polymers of

insulin was highly dependent on the pH of the preparation. Therefore claim 1 should contain an indication of the pH of the parenteral insulin preparation claimed.

XI. The appellant (patentee) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or, subsidiarily, on the basis of any of the auxiliary requests 1 or 2, all requests filed during the oral proceedings before the board.

The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Main request - Claim 1

Amendments - Article 123(2) EPC

2. Amended claim 1 is based primarily on claims 1 and 17 of the application as published.

3. Claim 1 finds further direct basis in claims 4 and 5 of the application as published in the aspect of the specific Asp^{B28} human insulin whereby the concentration of the insulin compound is not indicated, in claim 14 in the aspect of the Zn content and on page 6, lines 1 to 3 in the aspect of the phosphate buffer.

4. In the context of Article 123(2) EPC, the parties have referred, besides to claims 15 and 16 of the application as published, to a passage on page 5, lines 18 to 25. This passage read:

"In a preferred embodiment of the invention the insulin preparation comprises:

60 to 3000 nmol/ml, preferably 240 to 1200 nmol/ml, of human insulin or insulin analogue or derivative,

10 to 40 µg Zn/100 U insulin, preferably 10 to 26 µg Zn/100 U insulin, and

0 to 5 mg/ml, preferably 0 to 4 mg/ml, of a phenolic compound.

As a phenolic compound, 0.5 to 4.0 mg/ml, preferably 0.6 to 4.0 mg/ml, of m-cresol or 0.5 to 4.0 mg/ml, preferably 1.4 to 4.0 mg/ml, of phenol, or a mixture thereof, is advantageously employed."

5. The board considers, however, that the subject-matter of claims 15 and 16 of the application as published suffices for the amendment concerning the mixture of phenolic compounds to comply with the requirements of Article 123(2) EPC. The dependency of claim 16 on claim 15 in the application as published and the explicit reference to a mixture of m-cresol and phenol unambiguously predetermine the notion "a phenolic compound" in claim 15 to be of generic nature and not to exclude the presence of different phenolic compounds in the insulin preparation.

6. In view of the above considerations, the board is satisfied that claim 1 complies with the requirements of Article 123(2) EPC.

Clarity - Article 84 EPC

7. The respondent has argued that claim 15 as originally filed and the passage on page 5, line 22, refer merely to "0 to 5 mg/ml, ..., of a phenolic compound". The upper range of 5 mg/ml in the amended claims 1 and 6 was therefore unclear as it referred to a total content of a mixture of more than one phenolic compounds (i.e. cresol and phenol).
8. The board considers, however, as reiterated in point 5, *supra*, that the dependency of claim 16 on claim 15 in the application as published and the explicit reference to a mixture of m-cresol and phenol in claim 16 predetermine the notion "a phenolic compound" in claim 15 unambiguously to be of generic nature and thus also to embrace different phenolic compounds present in the insulin preparation.
9. As follows from the above considerations claims 1 and 6 are clear pursuant to Article 84 EPC.

Inventive step - Article 56 EPC

10. The subject-matter of claim 1 pertains to an aqueous insulin preparation comprising, and being therefore not limited to, the following compounds: human Asp^{B28} insulin; glycerol; a halogenide (5 to 100 mM of e.g. NaCl); a mixture of m-cresol and phenol (at least

0.5 mg/ml each and maximum 5 mg/ml in total); 10 to 40 µg Zn/100 U insulin; and a phosphate buffer.

The goal of the invention in the patent in suit is set out in paragraph [0017]: "*The ... insulin preparation has a high chemical stability which e.g. is reflected in a reduction in the formation of dimers and polymers and desamido insulins after storage. Furthermore, the physical stability is not deteriorated by the presence of the rather low amount of halogenide, and the insulin does not precipitate by long-term storage of the insulin preparations.*"

11. For assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art. In accordance with the established case law of the boards of appeal, the closest prior art is a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention.
12. The parties to the present appeal have considered various documents during the appeal proceedings to represent the closest prior art.
13. The appellant considered document (D1) to represent the closest prior art. It discloses parenteral pharmaceutical preparations of insulin which are less prone to precipitate under constant delivery conditions.

In column 3, lines 35 to 40, the document discloses that "[p]referably, the total molar concentration of ... sodium salts, does not exceed 0.01 [molar] and the presence of calcium or magnesium precipitating or complexing anions, such as phosphate ..., is avoided in the insulin solutions of this invention.". The board therefore notes that document (D1) quite explicitly advises the skilled person not to use phosphate buffer, a feature of the claimed invention, in the insulin preparation.

14. The respondent has considered either of documents (D1), (D3) and (D12) to represent the closest prior art.

Document (D3) discloses methods for preventing denaturation of aqueous insulin in pharmaceutical preparations by the addition to the solution of a surface active polymeric substances with alternating hydrophobic and hydrophylic zones (see column 3, lines 16 to 22). The insulin solutions for therapeutic purposes in accordance with document (D3) are prepared by dissolving up to 1,500,000 I.U. of bovine, swine or human insulin and which contain up to 0.8% by weight of zinc in 400 ml of water with the addition of HCl. This solution is then mixed with 500 ml of a solution which contains a preservative, for example phenol, cresol or methyl p-hydroxybenzoate, an agent for rendering the solution isotonic, for example sodium chloride, glycerol, glucose, or a similar carbohydrate, and a salt for buffering the pH value, for example sodium phosphate, acetate, citrate, sodium veronal, or tris(hydroxymethyl)-aminomethane and the pH adjusted to 3.0-4.0 or 6.8-7.5. 50 ml of an aqueous solution

containing 2 to 200 mg of a surface-active substance according to the invention are then added and the solution is made up to 1000 ml with water (column 5, lines 30 to 52). Example 9 of document (D3) specifies such a solution: "*Amorphous bovine insulin (1,000,000 I.U.) containing 0.8 percent by weight of zinc was dissolved in 400 ml of water with the addition of 5 ml of 1N hydrochloric acid. 500 ml of a solution of 2.5 g of phenol, 16 g of glycerol and 1.78 g of Na₂HPO₄.2H₂O were added to this solution. The pH of the solution was adjusted to 7.2-7.5. After adding 5 ml of an aqueous 0.1% strength solution of linear polypropylene glycol with an average molecular weight of 1.750 (Dalton), the mixture was made up to 1,000 ml with water and the solution was sterile-filtered.*".

Document (D12) demonstrates by physico-chemical studies that the self-association of insulin can be drastically altered by substitution of one or more key amino acids (abstract, lines 21 to 23) which is said to be important for future diabetes therapy (page 527, right-hand column, lines 47 to 54). Association was studied by circular dichroism, size-exclusion chromatography and ultracentrifugation (abstract, lines 5 to 7). One of the low self-association insulins prepared was human Asp^{B28} insulin (see e.g. the section "Preparation of analogs" bridging the columns on page 528). The results show that certain analogs, including Asp^{B28} insulin, demonstrate significant Zn-induced association, but less than native insulin (see page 530, right-hand column, lines 28 to 30).

15. From the above analysis it can be taken that, rather than disclosing pharmaceutical preparations, (D12) discloses insulin preparations in a physico-chemical context. Both documents (D1) and (D3) on the other hand disclose pharmaceutical insulin preparations with an aim to improve the insulin stability characteristics. The board notes however that document (D1), in column 3, lines 35 to 40, advises explicitly against the use of phosphate in the disclosed pharmaceutical insulin preparations. Therefore, in view of the above principles, the board considers that the disclosure representing the closest prior art for the purpose of the assessment of inventive step of the subject-matter of claim 1 is document (D3).

16. The parties and the board are in agreement that the technical difference between the insulin preparation disclosed in document (D3) and the subject-matter of claim 1 are the presence in the claim of the human Asp^{B28} insulin analog as active ingredient and the addition of m-cresol.

17. In order to formulate the problem to be solved by the subject-matter of claim 1 it needs to be established what the effect is of the dual choice of the human AspB28 insulin and the addition of cresol over the insulin preparation disclosed in closest prior art disclosure document (D3).

18. Concerning the choice of the active insulin ingredient of the preparations of the invention, the patent in suits sets out in paragraphs [0020] and [0022] that either fast-acting insulin analogues, such as human

AspB28 insulin, or insulin derivatives with a protracted profile of action can be used.

Concerning the phenolic compound in the preparation the patent in suit sets out in paragraph [0027] that either m-cresol, phenol or a mixture thereof is advantageously employed.

19. In its grounds of appeal the appellant has specifically addressed the effect of the combination of Zn-complexed AspB28 human insulin combined with phenol and m-cresol (final paragraph of page 11) and has thereby referred to document (D9), a post-published document. Document (D9) explained that the Asp^{B28} insulin analogue was a monomeric, rapid-acting hormone for therapeutic purposes having a mutation at the dimer-forming surface of the insulin monomer. The mutation was effective in destabilising the insulin dimer, giving rise to an essentially monomeric insulin at physiological concentrations. It was argued that the document thus confirmed that that the Zn-complexed Asp^{B28} human insulin in combination with phenol and m-cresol provided a rapid-acting preparation. As far as stability was concerned phenol was the preferred additive. However, considering the requirements for a satisfactory preservation, its sole use did not provide a sufficient effect. Hence it had been found that a combination of phenol and m-cresol gave a satisfactory result. The latter statement was essentially repeated in later stages of the proceedings (e.g. letter dated 6 February 2008, point 6.3, 3rd paragraph) when stating that a combination of phenol and m-cresol had been found to be necessary for a satisfactory preservation of the Zn-complexed Asp^{B28} human insulin.

20. In view of the above submissions by the appellant the problem to be solved by the claimed subject-matter must therefore be to provide for an alternative insulin preparation to the preparation disclosed in example 9 of document (D3) having improved stability characteristics and having satisfactory preservation characteristics in terms of anti-microbial action.

21. Human AspB28 insulin had been known in the prior art as an insulin with a diminished self-association, and a higher stability, i.e. an important feature for future diabetes therapy (see e.g. document (12), page 527, right hand column, lines 47 to page 528, left hand column, line 2).

The appellant has however argued that the choice of human Asp^{B28} insulin for parenteral insulin preparations was not obvious in the light of the document (D6), disclosing insulin analogues with a low ability to associate with a positively charged amino acid at the B28 position, rather than e.g. a negatively charged Asp.

The board notes however in this context that in view of the disclosure in document (D12), the skilled person would find itself not being confronted with a prejudice in the art which would prevent experimentation with the Asp^{B28} human insulin analog disclosed therein.

22. From document (D11), a review article on the topic of the galenics of insulin, especially from its tables 4 and 8, it can be taken that the preserving agents in therapeutic insulin preparations vary and range routinely from the use of methylparaben over the use of

phenol alone or in combination with the former with m-cresol. The board notes that this fact finds confirmation in document (D8) on page 425, left hand column, lines 38 to 48, where it is stated that newly registered human insulin preparations contain powerful phenol derivatives (addition of 0,06% Phenol and 0,15-0,25% m-cresol), which had already at an early time been applied as anti-bacterial agents.

23. Hence, for the formulation of therapeutic insulin preparations as well the use of human Asp^{B28} insulin as the combined use of anti-bacterial agents phenol and m-cresol was known in the prior art.

24. It is established case law of the boards of appeal (see Case Law of the Boards of Appeal, 2006, I.D.8.2.1) that in assessing the inventive step involved in an invention based on a combination of features, consideration must be given to whether or not the state of the art was such as to suggest to a skilled person precisely the combination of features claimed. The fact that an individual feature or a number of features were known does not conclusively show the obviousness of a combination. The question is not whether the skilled person, with access to the entire prior art, could have made the combination according to the invention, but whether he actually would have done so in expectation of an improvement. Indeed, were this not so, it would be impossible for a combination consisting of known individual features to involve an inventive step. The existence of a combination invention requires that the relationship between the features or groups of features be one of functional reciprocity or that they show a

combinative effect beyond the sum of their individual effects.

A mere aggregation of features must, however, be distinguished from a combination invention. Indeed, it has been established by the boards (see Case Law of the Boards of Appeal, 2006, I.D.8.2.2) that in patent law terms, the existence of a combination of features, i.e. of a combination invention, is to be viewed differently from the mere existence of partial problems, i.e. of an aggregation of features. According to current case law, partial problems exist if the features or sets of features of a claim are a mere aggregation of these features or sets of features which are not functionally interdependent, i.e. do not mutually influence each other to achieve a technical success over and above the sum of their respective individual effects, in contrast to what is assumed in the case of a combination of features.

25. The board notes that none of the experimental reports submitted by the appellant constitute, nor that the patent in suit discloses, comparative tests representing a fair comparison of the claimed subject-matter with respect to the closest prior art evidencing a mutual influence of both features leading to a technical success over and above the sum of the respective individual effects.

26. Accordingly, the board cannot identify a relationship between the features distinguishing the subject-matter of claim 1 from the insulin preparation defined in example 9 of the document representing the closest prior art which could be defined as one of functional

reciprocity or that they show a combinative effect beyond the sum of their individual effects. Indeed, both the selection of the human Asp^{B28} insulin as more stable insulin as the native bovine insulin of document (D3) and the combined use of phenol and m-cresol as preservative had plainly been suggested in the art in the context of pharmaceutical insulin preparations. The combination of these features in claim 1 therefore constitutes a mere aggregation of features which cannot form the basis for the acknowledgement of an inventive step.

27. In view of the above considerations, the subject-matter of claim 1 of the main request lacks an inventive step (Article 56 EPC).

First auxiliary request

Amendments - Article 123(2) EPC

28. Claims 1 to 5 are identical to claims 1 to 5 of the main request but for the wording "1. A parenteral pharmaceutical formulation consisting of an aqueous insulin preparation consisting of: ..." (emphasis added by the board) in claim 1, i.e. a change of the "comprising" wording to the "consisting of" wording.
29. The meaning of the word "comprising" is generally interpreted as encompassing all the specifically mentioned features as well as optional, additional unspecified ones, whereas the term "consisting of" only includes those features as specified in the claim. Therefore, "comprising" includes as a limiting case the composition specified by "consisting of". The board is

satisfied, therefore, that the amendment from the former into the latter does not extend beyond the content of the application as originally filed (see also e.g. decisions T 457/98 of 6 February 2001, point 2.1.1 and T 425/98 of 12 March 2002, point 3.1).

Inventive step (Article 56) EPC

30. Document (D1) discloses in example 1 a porcine Zn-insulin preparation, NaCl, glycerol and phenol and the pH was adjusted by NaOH. The parenteral preparation of claim 1 differs therefore from this disclosure in the aspects of the specific use of the human AspB28 analogue instead of the bovine insulin, the addition of m-cresol and use of a phosphate in the preparation. On the other hand, the wording "consisting" causes the subject-matter of claim 1 to differ from the insulin preparation in document (D3), by the substitution of the bovine insulin for the human AspB28 analogue, by the omission of the polypropylene glycol and by the addition of m-cresol.

31. Accordingly the change starting from document (D1) is the substitution of the active compound and the addition of two compounds, whereas the change starting from the disclosure in (D3), representing the closest prior art for the assessment of the invention in the main request, is the substitution of the active compound, the addition of one compound and the omission of an other compound. In view of the prudent nature of the skilled person when setting out to experiment with modifying the state of the art to solve technical problems encountered, the board considers that, rather than omitting specific compounds from prior art

preparations, he would experiment with gradually adding further compounds to existing preparations, with a view of not generating unforeseen adverse effects created by the absence of compound though necessary in the prior art preparations. In case of the present invention therefore the board considers document (D1) to represent the closest prior art.

32. Starting from document (D1) the board considers the problem to be solved as the provision of alternative human insulin preparations having improved stability characteristics over those disclosed in document (D1).
33. As reiterated before, the board notes that in column 3, lines 35 to 40, document (D1) explicitly advises the skilled person not to use phosphate buffer in the human insulin preparations disclosed.
34. The board therefore considers that the skilled person, when starting from the disclosure of document (D1) would not as a matter of routine experimentation both change the active ingredient of the insulin preparation and, against the explicit advice in document (D1) itself, buffer the solution with a phosphate buffer in order to solve the problem to be solved.
35. In view of the above considerations the subject-matter of claim 1 was not rendered obvious by the prior art. Seeing that claims 2 to 5 depend on claim 1, their subject-matter is neither rendered obvious. The subject-matter of claims 1 to 5 therefore involves an inventive step.

Sufficiency of disclosure

36. The respondent has argued that from Figure 4 in document (D4) it could be taken that the formation of covalent dimer and polymers of insulin was highly dependent on the pH of the preparation. Therefore claim 1 should contain an indication of the pH of the parenteral insulin preparation claimed.
37. The board construes this objection as one that claim 1 lacks essential technical features. However, such an objection pertains not to the question of reproducibility of the invention and therefore sufficiency of disclosure within the meaning of Article 83 EPC, for which the disclosure as a whole is the criterion, but to an objection under Article 84 EPC, which is not a ground for opposition. Only for this reason this objection must fail.
38. In view of the above considerations the board is satisfied that claims 1 to 5 of auxiliary request 1 satisfy the requirements of the EPC.

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 first auxiliary request as filed during the oral proceedings before the board (claims 1 to 5) and a description yet to be adapted thereto.

The Registrar

On behalf of the Chair
(Article 8(3) RPBA)

P. Cremona

B. Claes