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D E C I S I O N
of 14 July 2005

Case Number: T 0401/01 - 3.3.9

Application Number: 87110307.3

Publication Number: 0253395

IPC: A23J 1/20

Language of the proceedings: EN

Title of invention:
A process for producing bovine lactoferrin in high purity

Patentee:
MORINAGA MILK INDUSTRY CO., LTD.

Opponents:
01. Société des Produits Nestlé S.A.
02. Krayer, Warner Dirk

Headword:
-

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - yes"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0401/01 - 3.3.9

D E C I S I O N
of the Technical Board of Appeal 3.3.9
of 14 July 2005

Appellant: (Opponent 02)	Krayer, Warner Dirk c/o Koninklijke Nederlandse Zuivelbond FNZ Volmerlaan 7 NL-2280 HV Rijswijk (ZH) (NL)
Representative:	Smulders, Theodorus A.H.J., Ir. Vereenigde Postbus 87930 NL-2508 DH Den Haag (NL)
Respondent: (Proprietor of the patent)	MORINAGA MILK INDUSTRY CO., LTD. 33-1 Shiba 5-chome Minato-ku Tokyo-to 108-0014 (JP)
Representative:	Ebner von Eschenbach, Jennifer LADAS & PARRY LLP Dachauer Strasse 37 D-80335 München (DE)
Party as of right: (Opponent 01)	Société des Produits Nestlé S.A. 55, Avenue Nestlé CH-1800 Vevey (CH)
Representative:	-

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 9 February 2001 concerning maintenance of European patent No. 0253395 in amended form.**

Composition of the Board:

Chairman: P. Kitzmantel
Members: J. Jardón Alvarez
M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The grant of European patent No. 0 253 395 in respect of European patent application No. 87 110 307.3 in the name of MORINAGA MILK INDUSTRY CO., LTD. which had been filed on 16 July 1987, was announced on 30 October 1991 (Bulletin 91/44) on the basis of 6 claims, Claim 1 reading as follows:

"1. A process for producing bovine lactoferrin in high purity from raw milk-materials containing skim milk or whey originated from cow's milk which comprises:

(a) adsorption step wherein said raw materials are contacted, at a temperature between 0 - 60 °C, with weakly acidic cation-exchanger which includes carboxymethyl groups as ion exchanging groups and has haemoglobin adsorbing property more than 3.5 g/100 ml of the Na form of swelled cation-exchanger at 25 °C;

(b) rinsing step wherein said exchanger is washed with water to remove substances other than those adsorbed to said exchanger; and

(c) desorption step wherein the substances adsorbed to said exchanger are described [sic; should read: desorbed] therefrom with a solution of one or more of salts to thereby yield highly purified bovine lactoferrin."

II. Two Notices of Opposition requesting the revocation of the patent in its entirety on the grounds of Article 100(a) EPC were filed against this patent by:

Société des produits Nestlé S.A. (Opponent 1) on 23 July 1992 and

Krayer, Warner Dirk (Opponent 2) on 29 July 1992.

The oppositions were supported by the following documents:

D1: Law, B.A. and Reiter, B.: "The isolation and bacteriostatic properties of lactoferrin from bovine milk whey", Journal of Dairy Research (1977), 44, 595 - 599 and

D2: Zagulski, T., Jarzabek, Z., Zagulska, A. and Jedra, M.: "A simple method of obtaining large quantities of bovine lactoferrin", Prace i Materialy Zootechniczne (1979), 20, 87 - 101.

By its first decision announced orally on 28 September 1994 and issued in writing on 13 October 1994, the Opposition Division revoked the patent for lack of novelty of Claims 1 and 4 of the then main request over the disclosure of document D2 and for lack of compliance with the requirements of Article 123(2) EPC of the then auxiliary requests I, II and III.

III. During the subsequent first appeal proceedings this first decision of the Opposition Division was set aside by the appeal decision T 972/94 of 11 February 2000. The deciding Board held that the new main request filed on 9 February 2000 satisfied the requirements of Articles 54, 84 and 123(2) and (3) EPC. Since the Opposition Division had not dealt with the issue of inventive step, the Board made use of its power under Article 111(1) EPC and remitted the case to the

Opposition Division for further prosecution of the issue of inventive step.

IV. At the end of the resumed first instance proceedings, by an interlocutory decision announced orally on 17 January 2001 and issued in writing on 9 February 2001, the Opposition Division decided that the patent as amended in accordance with Claims 1 to 3 underlying decision T 972/94 met the requirements of the EPC, because the claimed subject-matter was inventive over the cited prior art.

The Opposition Division considered the method of obtaining lactoferrin as disclosed in D2 as the closest prior art. In the opinion of the Opposition Division, the technical problem to be solved by the patent in suit was the provision of an alternative process for producing lactoferrin of high purity. The decision held that the solution to this problem, namely the avoidance of the use of a buffer, represented a prima facie inventive alternative to the process of D2. It was held that there was no incentive in the prior art to leave out the buffer and consequently the subject-matter of the claims involved an inventive step.

Independent Claims 1 and 3 on which the decision was based read as follows:

"1. A process for producing bovine lactoferrin in high purity from raw milk materials containing skim milk or whey originating from cow's milk which process consists of:

(a) an adsorption step wherein said raw materials are contacted at a temperature between 0-60 °C with a

weakly acidic cation-exchanger which includes carboxymethyl groups as ion exchanging groups and which has an haemoglobin adsorbing property of more than 3.5g/100 ml of the Na form of the swelled cationic-exchanger at 25 °C,

(b) a rinsing step wherein said exchanger is washed with rinsing means, said rinsing means consisting of water to remove substances other than those adsorbed to said exchanger, and

(c) optionally a washing step wherein said exchanger is washed with further washing means, said further washing means being a relatively weak salt solution within a concentration range of 0.4-2.5 wt.% consisting of one or more of salts selected from the group consisting of sodium chloride, potassium chloride, calcium chloride and magnesium chloride to remove contaminants, and

(d) a desorption step wherein the substances adsorbed to said exchanger are desorbed therefrom with desorbing means, said desorbing means being a salt solution consisting of one or more salts selected from the group consisting of sodium chloride, potassium chloride, calcium chloride and magnesium chloride to thereby yield highly purified bovine lactoferrin, wherein the purity of the yielded bovine lactoferrin i.e. proportion (%) of lactoferrin to total proteins in the final product is equal to or more than 80% of the total proteins desorbed from said exchanger, wherein when said optional washing step is undertaken, said desorbing means is a relatively strong salt solution within a concentration range of 1.5-12 wt% consisting of one or more salts selected from said group of salts.

3. A process for producing bovine lactoferrin in high purity from raw milk materials containing skim milk or whey originating from cow's milk which process consists of:

(a) an adsorption step wherein said raw materials are contacted at a temperature between 0-60 °C with a weakly acidic cation-exchanger which includes carboxymethyl groups as ion exchanging groups and which has an haemoglobin adsorbing property of more than 3.5 g/100 ml of the Na form of the swelled cationic-exchanger at 25 °C,

(b) a rinsing step wherein said exchanger is washed with rinsing means, said rinsing means consisting of water to remove substances other than those adsorbed to said exchanger; and

(c) a washing step wherein said exchanger is washed with further washing means, said further washing means being a relatively weak salt solution within a concentration range of 0.4-2.5 wt.% consisting of one or more salts selected from the group consisting of sodium chloride, potassium chloride, calcium chloride and magnesium chloride to remove contaminants; and

(d) a desorption step wherein the substances adsorbed to said exchanger are desorbed therefrom with desorbing means, said desorbing means being a relatively strong salt solution prepared within a concentration range of 1.5-12 wt% consisting of one or more salts selected from those described in step (c) above, wherein the said purity of the yielded lactoferrin i.e. proportion (%) of lactoferrin to total proteins in the final product

is equal to or more than 95% of the total proteins desorbed from said exchanger."

V. On 2 April 2001 the former Opponent 2 (Appellant) lodged an appeal against the decision of the Opposition Division and paid the appeal fee on the same day.

In the Statement of Grounds of Appeal filed on 12 June 2001, the Appellant stated that the subject-matter of the claims did not involve an inventive step and filed a new document in support of its arguments:

D5: Lehninger, A.L. Biochemistry 2nd Edition. "The Molecular Basis of Cell Structure and Function" 1975, pages 167 to 168.

VI. By letter dated 28 September 2001 the Respondent (Patent Proprietor) requested that the appeal be dismissed and that the European patent be maintained in the form as amended during the opposition proceedings and upon which the interlocutory decision of the Opposition Division was based.

VII. On 1 March 2005 the Board dispatched the summons to attend oral proceedings on 14 July 2005 and, with the annexed communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal, drew the attention of the parties to the points to be discussed during the oral proceedings.

VIII. The former Opponent 1 did not file any substantive submissions or requests during the present appeal proceedings. By letter dated 19 May 2005 it informed the Board that it would not attend the oral proceedings.

IX. Oral proceedings before the Board were held on 14 July 2005 in the presence of the Respondent. The Appellant had informed the Board by letter dated 18 May 2005 of the withdrawal of its request for oral proceedings and of its intention not to attend the oral proceedings.

X. The Appellant's arguments were filed in writing with the Grounds of Appeal. They may be summarised as follows:

- The conclusion in the attacked decision that the novel and inventive step of the claimed process resided in the complete giving up of any pH control was not correct. The claimed process certainly did not dispense with pH control as this feature was not explicitly defined in the claims and there was a substantial difference between the pH of an alkali metal solution and an alkaline earth metal solution.

- The use of either a pH gradient or an ionic strength gradient were considered as equivalent methods for the resolution of a protein mixture into its individual components, as described on page 168 of D5, and consequently the claimed process was an obvious alternative to the process known from D2.

- In any case, the lack of an incentive to give up pH control could not be automatically considered as an indication of inventive step; it would be necessary to show evidence of overcoming a technical prejudice or other additional circumstance leading to the acknowledgement that the novel process was more than just an obvious alternative.

XI. The Respondent's written and oral submissions may be summarised as follows:

- The subject-matter of the claims was clearly distinguished from the art as disclosed in D2. While in the process of D2 the desorption step was carried out with a phosphate buffer solution (at pH 7,0), the claimed process employed a desorbing means consisting of a solution of one or more of the specified chloride salts, and thus buffers were excluded. Moreover, the further washing step (c) according to Claims 1 and 3 did not employ a buffer solution.

- The Respondent pointed out that the claimed process yielded a lactoferrin of higher purity than the lactoferrin prepared by the process of D2, but accepted that this interpretation was not supported by the documents on file. In its opinion the problem to be solved by the patent in suit vis-à-vis D2 was to provide an alternative, less complicated, process for the preparation of lactoferrin.

- This problem was solved by the claimed method wherein the various steps were performed at the environmental pH of the cation-exchanger using specified salt solutions as desorbing means in the absence of a buffer and without an additional ion-exchange purification step.

- There was no hint of this solution in the cited prior art. In particular the disclosure of D5 only described the basic principles of pH gradient

elution and ionic strength gradient elution which were well known to those skilled in the art. These consistently comprised the use of a buffer as an essential feature of the isolation of proteins, as set out on page 28 and section 7.2, pages 33 to 35 of D4.

D4: Ion Exchange Chromatography, principles and methods; Pharmacia Fine Chemicals AB, 1980, pages 3 to 71.

XII. The Appellant requested that the decision under appeal be set aside and that the European patent No. 0 253 395 be revoked.

The Respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. The only issue in the present appeal is that of inventive step (*Article 56 EPC*).

2.1 The patent in suit concerns a process for producing bovine lactoferrin of high purity. The process as claimed in independent Claims 1 and 3 includes four basic steps:

(a) an adsorption step using a weak acidic cation-exchanger,

(b) a rinsing step wherein the exchanger is washed with rinsing means consisting of water to remove substances not adsorbed,

(c) a washing step using a salt solution consisting of one or more salts selected from the group consisting of sodium chloride, potassium chloride, calcium chloride and magnesium chloride to remove contaminants (this step is optional in Claim 1 and mandatory in Claim 3), and

(d) a desorption step using as desorbing means a salt solution consisting of one or more salts selected from the group consisting of sodium chloride, potassium chloride, calcium chloride and magnesium chloride to obtain purified lactoferrin.

The process allows the preparation of lactoferrin with purity greater than 80% (see examples; purity being defined as proportion (%) of lactoferrin with respect to the total proteins desorbed).

2.2 *Closest prior art*.

2.2.1 The Board agrees with the finding in the decision under appeal that D2 represents the closest state of the art.

2.2.2 D2 discloses on page 88 and in the first paragraph of page 89 a method of obtaining large quantities of highly purified lactoferrin from bovine milk using a weak acidic cation-exchanger (CM-Sephadex C-50).

The process includes:

- an adsorption step using said cation-exchanger (step (a) of the patent in suit) to adsorb lactoferrin and lactoperoxidase,
- a rinsing step wherein the cation-exchanger is washed 3 times with deionised water (step (b)),
- a washing step wherein the cation-exchanger is washed 3 times with 0,02 M Na-phosphate buffer at pH 7,0 and another 3 times with 0,02 M Na-phosphate buffer + 0,15 M NaCl at pH 7,0 (step (c)),
- a first desorption step wherein the lactoperoxidase is washed out with 4 litres of 0,02 M Na-phosphate buffer + 0,3 M NaCl at pH 7,0 in a mixed vessel and with 0,02 M Na-phosphate buffer + 0,5 M NaCl at pH 7,0 in a simple vessel, and
- a second desorption step wherein the lactoferrin is washed out with several litres of 0,02 M Na-phosphate buffer at pH 7.0 + 0.5 M NaCl (step (d)).

The process allows the preparation of 40 to 45 grams of raw lactoferrin from 1000 litres of de-fated bovine milk of a calculated purity of about 62% (as calculated by the Patentee). A direct comparison of the purity of the lactoferrin prepared according to the process of D2 and the invention is not possible due to the different analytical methods employed as explained on pages 3 to 4 of the attacked decision.

Thus, while in the process of D2 lactoferrin is desorbed from the cation-exchanger with 0,02 M Na-phosphate buffer solution at pH 7,0 containing 0,5 M NaCl, in the claimed process lactoferrin is desorbed using a salt solution consisting of a solution of one or more of the specified chloride salts, thus

excluding the use of a buffer. Moreover, if in the claimed process a washing step is included, this step is also carried out with a solution of the specified chloride salts (step (c)).

2.3 *Problem to be solved and its solution*.

2.3.1 The technical problem underlying the patent vis-à-vis D2 is the provision of an alternative, less complicated, process for producing bovine lactoferrin in high purity.

2.3.2 This technical problem is solved by the process for producing bovine lactoferrin by the ion-exchange chromatography process as specified in Claims 1 and 3 and **without using any buffer solution**.

2.3.3 In view of the results of the examples, which show that lactoferrin of elevated purity can be obtained by the claimed process steps without using a buffer solution, the Board is satisfied that the above technical problem has effectively been solved by the claimed subject-matter.

2.4 *Inventive step.*

2.4.1 It remains to be decided whether, in view of the available prior art documents, it would have been obvious for the skilled person to solve this technical problem by the means claimed, namely by working without using a buffer solution.

2.4.2 From the documents cited during the opposition proceedings only documents D1 and D2 deal with the purification of lactoferrin. As explained above, in

document D2 the use of a buffer for controlling the pH is an essential feature of the process described therein.

Also, in D1 the purification of lactoferrin by cation-exchange chromatography using CM Sephadex C-50 is carried out using a buffer to control the pH in the desorption step. In D1 a tris/HCl buffer is used to maintain a pH of 8,0 (see paragraph bridging pages 595 to 596).

Thus, neither D1 nor D2 suggests the possibility of working in the absence of such a buffer. On the contrary, maintaining a given pH is an essential feature of the purification processes disclosed therein. The possibility of renouncing such pH control by the use of specific salts is therefore not obvious to the skilled person from the teaching of these documents.

2.4.3 It was argued by the Appellant by reference to D5 that the use of a pH gradient and the modification of the ionic strength of the eluting solution were equivalent methods commonly used for the separation of proteins and that therefore the use of a salt solution was to be seen as an obvious alternative to the process of D2. The solution to the problem therefore lacked an inventive step.

The Board does not accept this argument. The absence of a buffer is not explicit in D5 and according to D4, which is considered to represent the common general knowledge in the art, the isolation of proteins is generally carried out in the presence of a buffer.

Furthermore, while it is true that for the specified adsorption/desorption steps the pH and the ionic strength of the solution play a role, in the purification of a specific protein several other factors are to be considered as well, for example the isoelectric point of the protein, the nature of the ion exchanger used, and the kind of impurities present. These circumstances make it difficult to foresee the impact of procedural changes on the behaviour of a protein during the chromatography process. It is not possible, therefore, to draw any compelling conclusion from the observation of a single procedural step in isolation.

Moreover, it is not possible to anticipate that the claimed method would be able to yield lactoferrin of very high purity without the further ion-exchange purification step which is necessary according to D2.

2.4.4 Hence, the Board considers that, in the light of the cited prior art and of the general knowledge common in the field, it would not have been obvious to a person skilled in the art, starting from the process of D2, to arrive at the process as claimed in Claims 1 and 3.

The subject-matter of Claims 1 and 3 thus involves an inventive step within the meaning of Article 56 EPC. Claim 2 is dependent on Claim 1 and therefore also satisfies the requirements of Article 56 EPC.

3. The patent in suit is accordingly maintained in the form as maintained by the Opposition Division.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

G. Röhn P. Kitzmantel