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Bezeichnung der Erfindung: Method for improved bovine milk production
Title of invention:
Titre de l'invention :

Klassifikation / Classification / Classement : A61K 37/36

ENTSCHEIDUNG / DECISION

vom / of / du 14 February 1989

Anmelder / Applicant / Demandeur : MONSANTO COMPANY

Patentinhaber / Proprietor of the patent /
Titulaire du brevet :

Einsprechender / Opponent / Opposant :

Stichwort / Headword / Référence : Milk production/Monsanto

EPÜ / EPC / CBE Art. 56

Schlagwort / Keyword / Mot clé : "Inventive step (denied), obvious to try - reasonable expectation of success"

Leitsatz / Headnote / Sommaire

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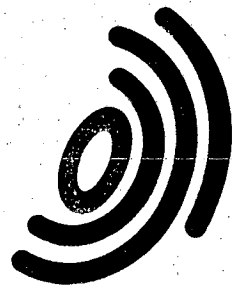

Case Number : T 249/88 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 14 February 1989

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Decision under appeal : Decision of Examining Division 001 of the European Patent Office dated 2 December 1987 refusing European patent application No. 83 870 003.7 pursuant to Article 97(1) EPC

Composition of the Board :

Chairman : K. Jahn
Members : R. Spangenberg
W. Moser

Summary of Facts and Submissions

I. European patent application No. 83 870 003.7 relating to a method for improved bovine milk production, filed on 14 January 1983 and claiming priority of 18 January 1982 from an earlier application in the United States of America, was refused by the Examining Division of the EPO by its decision dated 2 December 1987. This decision was based upon 4 claims of which Claim 1 as the only independent claim reads as follows:

"A method for increasing milk production by a cow which comprises administering to said cow, in an amount effective for increasing said production, a hormone which is a polypeptide having the amino acid sequence of pituitary bovine growth hormone with the addition of an N-terminal methionyl group, said hormone having been prepared by expression of a nucleotide sequence coding for said polypeptide, said sequence having been chemically synthesized or isolated from other bovine nucleotide sequences and then replicated."

II. The stated ground for the refusal was that the subject-matter of these claims did not involve an inventive step in the light of the disclosure in

(A) Insulins, Growth Hormone and Recombinant DNA Technology edited by John L. Guerignian, Raven Press, New York, 1981 pages 117-132,

(B) Proceedings of the Cornell Nutrition Conference, Feed Manuf. 1981, pages 47-51,

(C) Nature Vol. 293, No. 5831 (1 October 1981) pages 408-411, and

(D) J. Nutr. 1981, 111(9), pages 1662-71.

The Examining Division considered that the claimed subject-matter differed from the known art represented by (B) and (D) in that recombinant bovine growth hormone instead of natural bovine growth hormone is used for increasing the milk production of cows. Recombinant bovine growth hormone is chemically different from the native hormone since it contains an additional methionine in the N-terminal position. However it was already known from (A) and (C) to use in an analogous manner recombinant human growth hormone (hGH) instead of the natural hormone for stimulating growth.

The Examining Division also found that the last paragraph of (B) so strongly suggested the use of recombinant bovine growth hormone for increasing milk production that the person skilled in the art was in a "one-way street" situation leaving this use as the only logical possibility.

III. An appeal was lodged against this decision on 9 January 1988 and the appropriate fee paid on the same date. A Statement of Grounds of Appeal was filed on 31 March 1988.

In his written submissions and at the oral proceedings on 14 February 1989 the Appellant substantially argued that this last paragraph of (B) relates to bovine growth hormone (bGH) having the same amino acid sequence as pituitary bovine growth hormone, i.e. a copy of the natural product obtained by recombinant DNA technology, and submitted a declaration by Professor Baumann, the principal author of document (B) supporting this statement. Furthermore, the Appellant pointed out that, according to the application in suit, N-Met-bGH is however used and that therefore, the person skilled in the art was

not in a "one-way street" situation. He further argued that three generalisations were necessary if one were to conclude from documents A and C that it was obvious to use N-Met-bGH instead of bGH in a method for increasing milk production of a cow, since these documents relate to a different hormone (hGH, and not bGH), different animals (hypophysectomised rats, and not cows) and a different type of activity (growth promotion, and not increase of milk production). The fact that with respect to growth promotion, N-Met-hGH in hypophysectomised rats is equally active as pituitary hGH did not enable the skilled person to predict that N-Met-bGH would be active in increasing the milk production of a cow. The decision under appeal was therefore based on the knowledge of 1987 rather than on that of the priority date of 1982. Two further declarations by Dr. Krivi and Dr. Peel were filed supporting this submission.

The Appellant relied upon the decision T 02/83 (OJ EPO 6/1984, 265) and argued that a person skilled in the art would not have performed the claimed method. On the other hand, he confirmed that the test results contained in the application only reflect the higher purity of the recombinant hormone and that pure natural hormone has in fact the same activity as the recombinant bGH. He also admitted that, in the three declarations, the expression "predictability" was used in its strict scientific sense.

The Appellant requested that the decision under appeal be set aside and the patent be granted on the basis of the claims refused by the Examining Division.

At the end of the oral proceedings the decision was announced dismissing the appeal.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 EPC and Rule 64 and is, therefore, admissible.

2. The current version of the claims is properly based on the application document as filed and not open to formal objections. As this matter is neither disputed nor relevant to the announced decision, this need not to be explained in detail.

3. After examination of the cited prior art, the Board has reached the conclusion that the claimed subject-matter is novel. Since novelty has not been disputed by the Examining Division, it is not necessary to consider this matter in detail.

4. The closest prior art with respect to the claimed method is represented by (B) and (D) which both relate to a method for increasing the milk production of a cow by administering bGH. In these documents, natural (pituitary derived) growth hormone is used for this purpose. This hormone is obtained from bovine glands by a difficult purification process and, according to the Appellant's submission, was not sufficiently pure to obtain optimal and reliably constant results.

5. The technical problem with respect to this prior art may therefore be seen in providing an improved method for increasing the milk production of a cow.

According to the application in suit this problem is solved by administering recombinant N-Met-bGH instead of natural bGH. From the comparative data contained in the worked example (cf page 9 of the description), it can be seen that, in cows receiving the natural bGH, a 12.2% increase in milk production was observed, whereas, by administering the recombinant N-Met-bGH, an increase of

14% was obtained. The difference was statistically significant on the 95% probability level. Therefore, the technical problem underlying the application is plausibly solved.

6. In order to solve this problem, the person skilled in the art had a number of possibilities at hand. It can be seen from the description, page 1, lines 4 to 16, that not only the administration of bGH, but also the administration of other hormones such as prolactin, thyrotropin releasing hormone, thyroid stimulating hormone, estrogen or other materials such as prostaglandins or caseinate materials have also been envisaged as well as dietary optimisation, light cycle manipulation or udder massage.

Therefore, the present case in the Board's view does not belong to the extremely exceptional cases to which the decision T 192/82 (OJ EPO 9/1984, 415; "one-way street" situation) relates. Furthermore, even if the administration of bGH would have been the only method for increasing the milk production of a cow and the administration of recombinant bGH would have been the only reasonable way of improving this method as recommended in (B), this would leave a number of possibilities open since "recombinant bGH" may be produced by different techniques and does not necessarily possess the N-terminal methionine residue.

7. According to the Board's jurisprudence, the question to be answered when assessing inventive step is, as the Appellant rightly submits, whether a person skilled in the art would have considered the claimed method (see the decision T 02/83, OJ EPO 6/1984, 265, especially item 7 on page 270) in the expectation of some improvement or advantage in respect of the closest prior art represented by (B) and (D).

7.1 In the Board's view, the last paragraph of (B) contains a clear suggestion to choose a bGH produced by recombinant DNA technology for improving the milk production of a cow, since it is a general goal of recombinant DNA technology to provide high quantities of pure proteins which are otherwise only available with difficulty and in insufficient quantities from natural sources. In fact, this technology was developed in order to satisfy this need.

However, recombinant DNA technology does not necessarily yield the desired protein with an additional N-terminal methionine residue. For instance the DNA sequence corresponding to the desired protein may be added to the DNA sequence corresponding to a protein normally produced in the cell to be genetically modified. This cell will then produce a fusion protein containing both amino acid sequences which would be separated later on, e.g. by enzymatic cleavage. Another widely used method, however, is to incorporate the DNA sequence corresponding to the desired protein modified by the addition of the start codon (ATG) into E. Coli bacteria (see C, the summary of the beginning of the article). This method normally yields the desired protein carrying an additional methionine at the amino end. An identical copy of the natural protein may then be obtained by the additional step of removing the N-terminal methionine by enzymatic or chemical methods.

7.2 The production of recombinant bGH via a fusion protein would have first required the preparation of bacteria capable of producing such proteins. This is in principle possible, but very time-consuming. This was confirmed by the Appellant at the oral proceedings. N-Met-bGH however was more easily available because the required genetically modified bacteria already existed, see GB-A-1 565 190 (cited in the applicaiton in suit, in the paragraph

bridging pages 3 and 4). Removal of the terminal methionine from the available product, however, would also have included additional reaction and purification steps.

It is clear that such additional steps would take away a considerable part of the benefit involved in the use of the recombinant hormone instead of the natural bGH. Therefore, while this was not the only possibility in the sense of the "one-way street" situation underlying the decision T 192/82, in the Board's judgement there was a strong incentive to avoid such further steps or independent synthesis and to use the available product without further modification, at least if plausible reasons existed to expect that the desired improvement would be obtained.

7.3 This requirement is met since it is stated in (C), page 410 on the bottom of the right column that the authors of this article were not really surprised to find that the N-terminal methionine in N-Met hGH did not affect the biological activity because it was already known that in the natural hormone, which is not a homogeneous protein, the amino end is partially blocked, probably by an acetyl group. Similarly the expression "bovine growth hormone" is not applied to one single protein, but to a mixture of four main components (see page 4 of the amended description submitted on 15.5.1985). One of the modifications in the natural hormone is at the amino end which may be Phe or Ala-phe. In the latter case the amino acid sequence comprises 191 instead of 190 amino acids. Thus, in natural bGH the N-terminal Phe may also be acylated by an alanyl group, and the person skilled in the art had sound reasons to expect that the replacement of this alanine by methione would not affect the biological activity.

7.4 The person skilled in the art also had plausible reasons to expect a certain increase in activity in comparison with the natural hormone, since such an increase was suggested in (A) for the replacement of natural hGH by recombinant hGH (see the Chapter headed "Purity of bacteria-derived hGH, especially the sentence bridging pages 119 and 121) and was explained by the higher purity of the recombinant material. Therefore, the test results reported in the application in suit are not surprising, but only a confirmation of these expectations.

7.5 Furthermore, it was not the first time that a recombinant growth hormone containing an N-terminal methionine had been used instead of the natural hormone, albeit in different animals and with respect to a different type of activity, see (C) where recombinant human growth hormone was tested for growth promoting activity in hypophysectomised rats with the aim of eventually performing clinical tests (see page 411, the first paragraph on the left column). Nevertheless in the aspects of improving the purity and availability of the natural hormone the problems underlying (C) (see the abstract) and the application in suit are identical. It is quite clear from (C) that the situation was also similar insofar as no serious scientist, who is extremely cautious in such matters, could have predicted whether or not the recombinant hormone carrying the additional N-terminal methionine would be clinically useful. However, this fact did not prevent the authors of this article from testing the product directly, since this was the only way to find out whether this would be the case. Obviously these authors found it more reasonable to carry out these experiments than to undertake the additional step of removing the N-terminal methionine in order to obtain a product which is chemically identical to the natural hormone. Therefore, the Board cannot see any sound reason why a skilled person, faced with the similar technical

problem underlying the application in suit, would not have arrived at the same conclusion.

7.6 In view of this teaching, which is clearly derivable from the cited prior art, the Board is satisfied that a person skilled in the art would indeed have administered the available form of recombinant bGH, i.e. the N-Met-bGH obtained according to GB-A-1 565 190, without any modification to a cow in the reasonable expectation of obtaining the same or even a greater increase in milk production as observed when natural (pituitary derived) bGH is administered.

8. In the Appellant's opinion, the claimed method would not have been performed by a person skilled in the art because this person was not able to predict (in the strict scientific sense of this word) that N-Met-bGH would increase the milk production of a cow on the basis of documents (A) to (D) (see the three declarations submitted by the Appellant).

This opinion seems to imply that, since it was necessary to carry out a test in order to know with certainty whether or not N-Met-bGH would increase the milk production of a cow, the claimed method should have been regarded as unobvious because "obvious to try" is not the standard for assessing obviousness.

This objection is unjustified since, in accordance with patent jurisprudence, inventive step is not assessed from the view point of a highly specialised and outstanding scientist who, as is well-known, is extremely cautious with regard to unproven assumptions and, therefore, would be very reluctant to make a prediction in the absence of sufficient proof, but rather from that of the notional skilled person with his average ability and knowledge.

In the present situation, this notional skilled person was provided with a clear hint from the prior art pointing him in the direction of the claimed method, and it was only necessary to confirm experimentally that the highly probable result was in fact obtained. The necessity of experimentally confirming a reasonably expected result does not render an invention unobvious. Absolute predictability, especially in the field of biologically active chemical compounds, is rather exceptional, but inventions relating to such compounds and their administration to living organism may nevertheless be obvious. However, if such administration were to lead to unexpected results, which is not the case here, this may provide a basis for demonstrating unobviousness.

9. In the light of these explanations, the three declarations submitted by the Appellant do not provide evidence for the unobviousness of the claimed method.

9.1 Prof. Baumann, the principal author of (B), in his declaration only states that the reference in this document was not intended to imply that N-Met-bGH would be equivalent to the pituitary bGH and that he does not believe that anyone skilled in the art in 1981 would have interpreted the comment at the end of (B) as indicating an opinion that the authors expected that any recombinant bGH would be equally effective as pituitary bGH in enhancing milk production (item 3 and item 4, last paragraph). This means that this article is silent with respect to this question, but Prof. Baumann does not expressly state that he regards this result as unexpected or surprising.

In the second paragraph of item 4, Prof. Baumann states that the only way to establish whether N-Met-bGH is equally effective as pituitary bGH would have been to test it in lactating cows. However the declaration does not say that it was not a natural step in the technical

development, having regard to what is said in the preceding paragraphs to perform this test in a reasonable expectation of success and thereby to arrive at the claimed method.

9.2 The declarations of Dr. Peel and Dr. Krivi are mainly related to the question of predictability of the activity of N-Met-bGH in a strict scientific sense which is in the Board's view not critical for assessing inventive step in the present case. However, in Dr. Peels declaration some indications could be found which might have pointed away from testing recombinant bGH with the expectation of increasing the milk production of a cow. Thus, in items 2 and 3 of his declaration, Dr. Peel states that there were some indications in the literature that components other than somatotropin (bGH) were present in the natural preparations which may have contributed to the lactation enhancement. Studies had been published prior to January 1982 in which it was found that highly purified pituitary somatotropin had lost its ability to stimulate lipid mobilisation which was believed at that time to be the basis of the observed enhancement of lactation. Furthermore, at that time most of the experiments had been conducted with low producing cows and there was some doubt expressed that, given this association between lactation enhancement and the lipolytic effect, high producing cows would not experience the same degree of lactation enhancement (see item 4). However, these statements are superseded by (D), a document published in 1981 of which Dr. Peel is a co-author and which relates to the lactation enhancement of high producing cows (see the title). In this document it is stated that natural bGH in fact also enhances the milk production in the high-yielding dairy cows (see the abstract), and it can be inferred therefrom that this effect was not expected to disappear when highly purified bGH was used (see page 1163, left column, the first complete paragraph).

10. As no request has been made to consider the subject-matter of the dependent Claims 2 to 4 separately, these claims must fall together with Claim 1.

Order

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar: The Chairman: