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D E C I S I O N
of 16 April 1999

Case Number: T 0277/95 - 3.3.4

Application Number: 90118215.4

Publication Number: 0411678

IPC: C12N 15/16

Language of the proceedings: EN

Title of invention:
Method for the production of erythropoietin

Patentee:
GENETICS INSTITUTE, INC.

Opponent:
JANSSEN-CILAG GmbH
AMGEN INC.
HOECHST AG

Headword:
Production of erythropoietin/GENETICS INSTITUTE

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 87, 88, 114(2), 123(2), 123(3)

Keyword:
"Main request - broadening of scope of claims (no)"
"Added subject-matter (no)"
"Clarity (yes)"
"Right to priority (denied)"
"Novelty (yes)"
"Inventive step (yes)"
"Sufficiency of disclosure (yes)"

Decisions cited:
G 0002/88, G 0001/92, G 0009/92, T 0016/87, T 0081/87, T 0418/89, T 0412/93, T 0639/97

Catchword:
"Inherency" has to be established on the basis of certainty, not probability or possibility (cf point 15 of the reasons).

Europäisches Patentamt	European Patent Office	Office européen des brevets
Beschwerdekammern	Boards of Appeal	Chambres de recours

Case Number: T 0277/95 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 16 April 1999

Appellant: (Proprietor of the patent)
GENETICS INSTITUTE, INC.
87 Cambridge Park Drive
Cambridge, Massachusetts 02140 (US)

Representative:
Huber, Bernhard, Dipl.-Chem.
Patentanwälte
H. Weickmann, Dr. K. Fincke
F.A. Weickmann, B. Huber
Dr. H. Liska, Dr. J. Prechtel, Dr. B. Böhm
Postfach 86 08 20
D-81635 München (DE)

Respondent I: (Opponent 01)
JANSSEN-CILAG GmbH
Raiffeisenstr. 8
D-41470 Neuss (DE)

Representative:
Voelker, Ingeborg Carla Emmy, Dipl.-Biol.
Uexküll & Stolberg
Patentanwälte
Beselerstr. 4
D-22607 Hamburg (DE)

Respondent II: (Opponent 02)
AMGEN INC.
1900 Oak Terrace Lane
Thousand Oaks, California 91320 (US)

Representative:
Brown, John David
FORRESTER & BOEMERT

Franz-Joseph-Str. 38
D-80801 München (DE)

Respondent III: (Opponent 3)
HOECHST AG
D-65926 Frankfurt am Main (DE)

Representative:
Keller, Günter Dr.
Lederer, Keller & Riederer
Patentanwälte
Prinzregentenstr. 16
D-80538 München (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 6 April 1995 concerning maintenance of European patent No. 0 411 678 in amended form.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: L. Galligani
C. Holtz

Summary of Facts and Submissions

I. The appeal lies from the interlocutory decision of the opposition division issued on 6 April 1995 whereby the European patent No. 0 411 678, claiming priority inter alia from US 693 258 dated 22 January 1985 (third priority), was maintained in amended form on the basis of claims 1 to 7 for all designated States except AT (non-AT States), claims 1 to 6 for AT and an adapted description thereto, this being the second auxiliary request then on file. The said claims were as granted, the granted claims 8 to 11 having been deleted.

II. The opposition division decided that, while the said claims fulfilled the requirements of the EPC, the main request then on file, which comprised further claims 8 to 11 as granted for the non-AT States (claims 7 to 10 for AT), and the first auxiliary request, which also

comprised claims 8 to 11 for the non-AT States (claims 7 to 10 for AT), were not allowable under Article 54(3)(4) EPC having regard to the following document:

(1) EP-A-0 148 605.

III. Claim 8 (non-AT States) as granted read as follows:

"Recombinant human erythropoietin characterized by the presence of O-linked glycosilation, obtainable by the steps of

(a) culturing in a suitable medium CHO cells containing a DNA sequence encoding human erythropoietin said DNA sequence operatively linked to an expression control sequence and

(b) recovering and separating the EPO from the cells and the medium."

Dependent claims 9 to 11 (non-AT States) related to further embodiments of claim 8, claim 9 specifying that the glycosylation pattern comprised fucose, claim 10 reporting the relative molar levels of specific sugars and claim 11 stating the presence of N-acetyl-galactosamine.

IV. The appellant (patentee) lodged an appeal against the said decision and filed with the statement of grounds of appeal new documents, including two declarations of Dr A. Haselbeck.

V. Respondents I and II (opponents 01 and 02) replied to

the statement of grounds of appeal filed by the appellant. With their reply, respondents I filed a number of exhibits, including the following:

(E19) Sasaki H. et al., J. Biol. Chem., 1987, Vol. 262, pages 12059 to 12073.

VI. On 7 August 1997, the appellant filed a new main request and an auxiliary request.

VII. The board outlined the issues to be discussed in the communication dated 15 July 1998.

VIII. In reply thereto, on 24 September 1998 the appellant filed a new main request and four auxiliary requests in the two versions for non-AT States and AT.

The **main request** consisted of: claims 1 to 7 as granted and claims 8 and 9 for all non-AT States; the corresponding claims 1 to 6 for AT as granted and claims 7 and 8 for AT. Claims 8 and 9 for the non-AT States, which are identical to claims 7 and 8 for AT, read as follows:

"8. Method for producing recombinant human erythropoietin (hEPO) by the steps of

(a) culturing, in a suitable medium, CHO cells which contain, operatively linked to an expression control sequence, a DNA sequence encoding hEPO, and

(b) recovering and separating the recombinant hEPO produced from the cells and the medium,

characterized in that CHO cells are used which have the capability of producing N- and O-linked glycosylation, with incorporation of fucose and N-acetyl-galactosamine, and that recombinant hEPO with N- and O-linked glycosylation is recovered and separated from the cells and the medium."

"9. Method according to claim 8, wherein the recombinant hEPO has a glycosylation pattern comprising relative molar levels of hexoses to N-acetylglucosamine (Nacglc) of 1.4:1, specifically galactose: Nacglc = 0.9:1 and mannose: Nacglc = 0.5:1."

IX. All respondents filed comments in response to the board's communication.

X. Oral proceedings to be held on 24 November 1998 were rescheduled.

XI. On 15 March 1999 the appellant made new submissions with enclosures. Respondents II filed comments thereupon and submitted further evidence.

XII. Oral proceedings took place on 15 and 16 April 1999. Amended pages 2 and 3 of the description were filed.

XIII. In addition to the already cited document (1) and Exhibit 19 (E19), the following documents are referred to in the present decision:

(3) Dordal M. S. et al., Endocrinology, 1985, Vol. 116, No. 6, pages 2293 to 2299;

(4) Jacobs K. et al., Nature, 28 February 1985,

Vol. 313, pages 806 to 810.

XIV. The appellant argued that, since a CHO cell line expressing recombinant hEPO as described in the patent in suit had been made available by way of a deposit, the deposit thereof being already mentioned in the third priority document, claims 8 and 9 for the non-AT States (claims 7 and 8 for AT) were entitled to the priority date of the said priority document. In their view, for a skilled person, who could have taken a sample of the deposited cell line and analysed the recombinant hEPO thereby made, the subject-matter of the said claims was an inherent disclosure already provided in the third priority document (cf also point 14 of the reasons infra).

The appellant further submitted that document (1) could not be detrimental to the novelty of the method as now claimed because, apart from the many errors and inconsistencies in relation to the reported expression in CHO cells which rendered the Example 10 of this document not repeatable, it described a product which lacked fucose and N-acetylgalactosamine. Nor could the prior sale of a recombinant hEPO by the firm Amgen Inc. be detrimental to novelty as there was not a sufficient amount for any meaningful analysis and there was no link whatsoever with document (1).

XV. The respondents argued that the amended claims of the main request offended against Article 123(2) and (3) EPC as they relied on features (CHO cells having the capability of producing N- and O-linked glycosylation; recovery and separation of recombinant hEPO with N- and O-linked glycosylation) which were not disclosed in the

application as filed, and they covered subject-matter which was not covered by the claims as granted (eg unglycosylated recombinant hEPO) (cf also points 6 and 8 infra).

They further argued that the feature "which have the capability of producing N- and O-linked glycosylation" was vague, unclear and not supported by the patent specification (cf also point 10 infra).

They also submitted that the claimed method, which could not enjoy any of the priority dates, was not novel having regard to document (1) which contained in respect of the expression of recombinant hEPO in CHO cells the same technical information (in Example 10 the same known CHO cell line of Urlaub et al. was used as a host) and which, in view of the inherent capability of CHO cells to perform N- and O-linked glycosylation, necessarily resulted in a product with the same features. This was confirmed by a number of declarations on file, by the analysis of the prior sold product of the firm Amgen Inc. as well as by the finding of the board of appeal in the cases T 412/93 of 21 November 1994 and T 639/97 of 26 March 1998 (cf also point 18 infra).

As regards inventive step, the respondents presented essentially the following two lines of arguments:

(a) If document (1) was taken as the closest prior art and the problem was defined as producing biologically active recombinant hEPO, it had to be observed that the solutions offered by document (1) and by the patent in suit were

identical, the only difference being that the patent in suit spelled out the inherent glycosylation pattern of the product. The manifestly erroneous preliminary analysis reported in document (1) would not have been an impediment to further analysis as the problem had already been solved by providing a biologically active recombinant hEPO. By simply repeating the work described in document (1), the skilled person would have operated as set out in claim 8 at issue and would have obtained a product with the glycosylation pattern recited in the claim. There could be no inventive contribution in merely identifying the presence of N- and O-linked glycosylation.

(b) If document (4) was taken as the starting point, and the problem was defined as finding a stable system of expression, the obvious solution was the use of CHO cells as described in document (1). Document (4) had already implied that O-glycosylation could be present. This would have been looked for and would inevitably have been found, together with N-glycosylation, in the recombinant hEPO produced when working according to document (1). Thus, there was no inventive step in the claims at issue.

The respondents further submitted that, if the board could not agree with their view that the disclosure of the patent in suit was not essentially different from that of document (1), then it did not contain sufficient information that would lead one of ordinary skill to the product indicated in claims 8 and 9. In

particular, the information about the cells producing the recombinant hEPO which was analysed was confusing so that the reader did not know which cells produced the said specific glycosylation pattern and under which technical circumstances (cf also point 31 infra).

As regards the amendments to the description, the respondents considered that they did not adequately reflect the limited scope of claims 8 and 9 (cf also point 35 infra).

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

(1) claims 1-7 as granted, and
claims 8 and 9 as filed on 24 September 1998 for all non-AT States, the corresponding claims 1-6 for AT as granted and claims 7-8 for AT as filed on 24 September 1998 (main request), alternatively either of the auxiliary requests 1-4 for non-AT States and AT, respectively, also filed on 24 September 1998;

(2) pages 2 and 3 of the description as filed in the oral proceedings and pages 4-34 of the description as granted, and

(3) figures 1-8 as granted.

XVII. The respondents requested that the appeal be dismissed.

Reasons for the Decision

Late-filed documents

1. In its communication dated 15 July 1998, the board had fixed the final date for making further written submissions in preparation of oral proceedings at two months before the proceedings, which were to be held on 24 November 1998, and had drawn the parties' attention to the fact that facts and evidence presented after that date might be disregarded pursuant to Article 114(2) EPC.

2. On 24 September 1998, the appellant filed a reply to the said communication with new claim requests. Shortly before oral proceedings were to take place, they had to be rescheduled for 15 April 1999 (cf Section X supra). One month before this date, the appellant filed new evidence and, in reply thereto, respondents II submitted an affidavit. The newly filed documents were all in relation to the question of the carbohydrate constitution values given in Example 10 of document (1).

3. In consideration of the fact that the new documents were late-filed and that they were prima facie not more relevant than the abundant evidence already on file on the same issue, the board decided to disregard them under Article 114(2) EPC.

Extent of the appeal

4. The respondents did not challenge the decision by the opposition division to maintain the patent on the basis

of claims 1 to 7 for the non-AT States (claims 1 to 6 for AT) which are identical to claims 1 to 7 as granted (claims 1 to 6 for AT). Claims 1 to 7 (non-AT States; claims 1 to 6 for AT) of all requests on file are identical to the claims maintained by the opposition division and thus, under the ruling of decision G 9/92 (OJ EPO 1994, 875), they are not open to any objection.

Main request (Claims 8 and 9 for non-AT States = claims 7 and 8 for AT)

Articles 123(2) and (3) and 84 EPC

5. Claims 8 to 11 for non-AT States as granted were product-by-process claims directed to recombinant hEPO (cf Section III supra). The corresponding claims 7 to 10 for AT were drafted as method claims.

Claims 8 and 9 for the non-AT States at issue are directed to a method for producing recombinant hEPO. The process steps a) and b) recited in the preamble of claim 8 are the same as steps a) and b) recited in the granted claim 8. The characterising portion of the claim (not present in claim 8 as granted which was in a one-part form) now defines more specifically the CHO cells used and the product which is to be recovered and separated. The glycosylation pattern is further specified in dependent claim 9, which corresponds to claim 11 as granted.

The said claims 8 and 9 for non-AT States are identical to claims 7 and 8 for AT, thus, for the sake of simplicity, in the following discussion reference is made exclusively to claims 8 and 9 for non-AT States.

6. The respondents maintain that the claims at issue offend against Article 123(3) EPC because they cover populations of recombinant hEPO (eg unglycosylated Epo) which were not covered by the corresponding claims as granted.

7. The board observes that:

(a) Product claim 8 as granted, while being directed to recombinant hEPO characterised by the presence of O-linked glycosylation, did not exclude N-linked glycosylation. As a matter of fact, dependent claim 9 as granted referred to the presence of fucose, which is normally seen as an indication of N-glycosylation (cf declaration of Prof. Kamerling, page 12 of the English translation);

(b) Claim 8 at issue is directed to a method in which recombinant hEPO with N- **and** O-linked glycosylation with incorporation of fucose and N-acetylgalactosamine is recovered and separated. Under Article 64(2) EPC only a recombinant hEPO with these features is protected as being the direct product of the method (thus, **not** an unglycosylated product). The resulting product is more specifically, and thus more narrowly defined than that of claim 8 as granted. Consequently, also in accordance with the ruling of decision G 2/88 (OJ EPO 1990, 93), no breach of Article 123(3) EPC is seen by the board.

8. The respondents maintain that the claims at issue also offend against Article 123(2) EPC because the

application as filed does not refer to CHO cells having the capability of producing N- and O-linked glycosylation. They argue that neither direct nor indirect information is provided in respect of the selection of CHO cells having this feature.

9. The board observes that the application as filed provides examples of expression of hEPO in CHO cells (cf Examples 10 and 11), that the recombinant hEPO produced in Example 11 was analysed and found to bear N-linked glycosylation, as shown by way of selective enzymatic removal and subsequent SDS-PAGE analysis, **and** O-linked glycosylation, as shown by the presence of N-acetylgalactosamine (cf pages 13 and 14). The table on page 13 reports the relative molar level of the sugars in respect of N-acetylglucosamine, these being the values found in claim 9 at issue. On page 14, the results obtained are compared with those of a prior art recombinant hEPO. In particular, the presence of "reproducibly observable amounts of both fucose and N-acetylgalactosamine" is emphasized, these sugars being absent in the said prior art product. From the cited passages of the description of the application as filed, the skilled person would unambiguously derive that the stated and achieved aim of the invention is a general method for producing recombinant hEPO with N-**and** O-linked glycosylation with incorporation of fucose and N-acetygalactosamine and that this presupposes the use of CHO host cells having such activities. Thus, no breach of Article 123(2) EPC is seen by the board as the claims at issue do not contain subject-matter which extends beyond the content of the application as filed.

10. The respondents further consider that the feature

"which have the capability of producing N- and O-linked glycosylation..." lacks clarity and support in the description as, in their view, firstly, the said capability depends inter alia on the conditions of culture and, secondly, nothing is said in the patent specification as to how to achieve such a capability.

11. It is observed that the latter submissions are at odds with those made within the framework of the discussion of the substantive issues that the great majority of the CHO cells always perform N- **and** O-linked glycosylation (cf points 18 infra and Section XV, items a) and b) supra). Notwithstanding this, in the board's view, the skilled person can recognise the potential of a given CHO cell line to carry out N- and/or O-glycosylation by means of enzymatic tests (eg presence of glycosyltransferases). For example, by selective removal of the N- and/or O-linked sugar chains from a glycoprotein which is produced, and subsequent verification of changes in its molecular weight, or by establishing the presence of N-acetylgalactosamine residues (cf page 12 of the description of the patent in suit) the skilled person is able to assess the quality of a CHO cell line, ie its capability of performing N- **and** O-linked glycosylation vs the capability of performing only either one or none of these activities. For this reason, the said feature is considered to be sufficiently clear for the skilled person and there is no need to define it further in the claim in quantitative terms.

As for the issue of support of the claims by the description, the board notes that it is true that many

variables can influence the N- and/or O-glycosylation process in cells which have the glycosylation machinery therefor (cf eg Declarations of Drs S. Jeffcoate and A. G. Haselbeck). However, in the board's view, the skilled person, having being presented with the results of the patent specification and thus knowing what to look for (ie N- **and** O-glycosylation with incorporation of fucose and N-acetylgalactosamine), needed no detailed instructions as to the steps and conditions necessary in order to perform the invention in the broader outline of the claims (cf also "Sufficiency of disclosure", point 32 infra). Consequently, the requirements of Article 84 EPC are met.

Priority (Articles 87 and 88 EPC)

12. The right to priority is governed by Article 87 EPC which requires that the European patent application and the application whose priority is claimed relate to the **same invention**. According to Article 88(3) and (4) EPC the right of priority shall cover only those elements of the application which are **specifically disclosed as a whole** in the application whose priority is claimed.

13. The main criterion in respect of the question of entitlement to priority is whether the claimed invention is disclosed in the priority document as **a matter of substance, ie with all its essential features**. For example, in T 81/87 (OJ EPO 1990, 250) it was made clear that the disclosure of the essential elements must be either express, or be directly and unambiguously implied by the text, and that missing elements which are to be recognized as essential only

later on are thus not part of the disclosure.

14. In the present case, the appellant maintained that, since the deposited cell line CHO ATCC CRL8695, which was disclosed in Examples 10 and 11 of the third priority document, was the producer of the recombinant hEPO, of which the sugar composition analysis was reported only in the patent in suit (cf page 11, line 51 to page 12, line 20), the right of priority had to be acknowledged to the method claims at issue because the said biochemical information was "inherent" in the deposited cell line. In fact, the said cell line was available to the skilled person, and thus the recombinant hEPO it made would have revealed upon analysis its N- and O-linked glycosylation pattern. In this respect reference was made to the opinion of the Enlarged Board of Appeal G 1/92 (OJ EPO 1993, 277). The appellant also made reference to the later publication by Sasaki et al. (document (E19)) which demonstrated that production of recombinant hEPO by CHO cells in four different batches always resulted in products qualitatively similar in terms of the carbohydrate composition (cf Table I on page 12061).

15. The board does not share the appellant's view for the following reasons:

(a) Claims 8 and 9 are method claims, ie claims directed to **an activity which the skilled person can only perform if he or she is given the appropriate instructions**, these being, in particular, those recited in the characterising portion of claim 8, namely **(i)** use CHO cells which have the capability of producing N- and O-linked

glycosylation, with incorporation of fucose and N-acetylgalactosamine, and **(ii)** recover and separate from the cells and the medium a recombinant hEPO with N- and O-linked glycosylation. The claim construction itself indicates that the latter are the essential characterising features of the method. It should thus be possible, if the priority right has to be acknowledged, to derive them directly and unambiguously from the priority document as a whole. Otherwise, the priority right has to be denied.

(b) Nothing is found in the third priority document which relates to any desired or achieved glycosylation pattern of the recombinant hEPO produced by the deposited cells line. Those passages of the description of the application as filed which related to the sugar analysis and which have been considered by the board to provide support for the said features (i) and (ii) for the purposes of Article 123(2) EPC (cf point 9 supra), are not found in the priority document in question. This document does not describe how to recover and separate the recombinant hEPO from the cells and/or the medium, but merely its biological assay (cf Tables 10 and 11), and makes no mention of any sugar analysis of the expressed product.

(c) In spite of the availability of the deposited cell line, the skilled person, in the absence of any information about the presence of glycosylation and its pattern, cannot derive from the third priority document the specific instructions which characterise the method of the claims at issue

(cf item a) supra). Only if told what he or she is supposed to achieve can a skilled person devise a strategy to actually achieve it. In this sense, the essential elements of the claimed method are missing in the said priority document (cf point 13 supra).

(d) Opinion G 1/92 (supra) dealt with the issue of the composition or internal structure of a chemical product available on the market. The current claims under review are general method claims for producing recombinant hEPO in CHO cells. Therefore, G 1/92 cannot be properly applied by way of analogy to the present technical situation, as submitted by the appellant. This is because the skilled person cannot derive the relevant information about the glycosylation pattern from a direct analysis of the deposited cell line, but only from the analysis of the recombinant hEPO that the said cell line produces. To this extent he or she has first to culture the cells under appropriate conditions, and then recover and separate the product from the cells and the medium. Nothing is said about these steps in the priority document and thus the skilled person, who does not know which glycosylation pattern has to be achieved (cf item c) supra), has to rely on his or her own resources. As the ultimate glycosylation pattern of the recombinant hEPO which is produced is dependent upon many variables, such as the conditions of culture, the method of isolation etc. (cf Declarations of Drs S. Jeffcoate and A. G. Haselbeck), there is not the necessary certainty that a pattern as recited

in claims 8 and 9 at issue will necessarily be found. The later publication (E19), although showing that this can **often** be the case, does not prove that it is **always** the case. Under these circumstances, the board is unable to accept that the glycosylation pattern referred to in the claims at issue was "inherent" in the CHO cell line referred to in the priority document. "Inherency" has to be established on the basis of certainty, **not** probability or possibility.

16. For these reasons, claims 8 and 9 at issue are not entitled to the priority date of the third priority document, but only to the filing date of the European application, ie 3 December 1985.

Novelty (Article 54 EPC)

17. In view of the above finding on priority, document (1), published on 17 July 1985, is prior art under Article 54(2) EPC.

18. The respondents consider that document (1) affects the novelty of the claims 8 and 9 as it describes in Example 10 a process for producing and recovering from CHO host cells a recombinant hEPO with a glycosylation pattern, which, by virtue of the fact that the CHO cells are inherently capable of performing N- **and** O-linked glycosylation, falls within the terms of that recited in the said claims. In their view, this was shown by the declarations of Drs T. W. Strickland, J. K. Browne and L. Chasin as well by the analysis of the recombinant hEPO sold by the firm Amgen Inc. in 1985 prior to the filing date of the patent in suit

(cf "Report of the Monosaccharide Composition Analysis of the Oligosaccharides Associated with the Glycoprotein r-HuEPO, L07B" performed by Oxford GlycoSystems Ltd.). It was furthermore confirmed, in their opinion, by the findings of the board of appeal in the case T 412/93 (supra). The data reported in document (1) in relation to the carbohydrate analysis were irrelevant because, firstly, they were presented as being preliminary in document (1); secondly, they were so manifestly wrong that the then competent board of appeal decided to have the corresponding passage of the specification deleted when adapting the description of the patent maintained on the basis of document (1) (cf decision T 639/97 of 26 March 1998, in particular passage 5.3 of the reasons), and, thirdly, there were sufficient amounts of the product sold by the firm Amgen Inc. and made according to document (1) to allow it to be analysed correctly.

19. The board does not share the respondents' view for the following reasons:

(a) Document (1), although indeed describing the expression of recombinant hEPO in CHO cells, its recovery and preliminary analysis, including carbohydrate analysis, does not contain any explicit indication that: **(i)** specifically, CHO cells should be used which have the capability of producing N- **and** O-linked glycosylation, with incorporation of fucose and N-acetylgalactosamine, and **(ii)** precisely, a recombinant hEPO with N- **and** O-linked glycosylation should be recovered and separated from the cells and the medium. In decision T 412/93 (supra), the board did not

address specifically the question of the presence of N- **and** O-glycosylation, with presence of fucose and N-acetylgalactosamine. Rather, in the framework of the discussion of the reproducibility inter alia of Example 10, the board expressed the belief, that a recombinant hEPO made according thereto was expected to exhibit a proper glycosylation pattern and be active (cf point 106 of the reasons).

(b) It cannot be said that indications to operate in the specific manner indicated in claims 8 and 9 at issue could be derived by way of implication either from document (1) alone or in combination with the product sold by the firm Amgen Inc. in 1985 (cf advertisement in Nature Vol. 313, 28 February 1985). This is because, on the one hand, document (1), taken in isolation, pointed inter alia to the absence of N-acetylgalactosamine residues and thus rather indicated absence of O-glycosylation. The skilled person could possibly have some doubts about the absolute validity of the carbohydrate constitution values reported in Example 10, in particular in relation to the high hexose value of recombinant hEPO, which he or she might suspect was due to some contamination; however, the skilled person would have considered the data about the absence of fucose and N-acetylgalactosamine to be plausible, especially in view of the fact that no O-glycosylation had been detected either in the urinary Epo either (cf document (3)). On the other hand, there was no apparent link between the product sold by the firm Amgen Inc. and Example 10 of document (1) so as

inevitably to bring the skilled person, after an analysis of the product sold by the firm Amgen Inc. (of course, under the hypothesis that such an analysis was realistic and feasible in terms of amount available and costs), to the conclusion that the product of Example 10 was indeed N- **and** O-glycosylated with incorporation of fucose and N-acetylgalactosamine. The skilled person would have taken the disclosure in document (1) at its face value and seen no need for an analytical verification of the results.

(c) From the information given by the firm Amgen Inc. to the public with the prior sale of hEPO per se (cf advertisement in Nature referred to in item b) supra) the skilled person could not derive any teaching about the method of preparation.

20. Thus, the board has to conclude that the method of claims 8 and 9 was anticipated neither by the disclosure of document (1) nor by the prior sale of recombinant hEPO by the firm Amgen Inc.

21. No other prior art document was cited as being detrimental to the novelty of claims 8 and 9 by the respondents. The board is also of the opinion that none of the other documents on file affects the novelty of the said claims.

Inventive step (Article 56 EPC)

22. In the board's view, the closest prior art document is represented by document (1) which, as already stated (cf point 19 supra), describes in Example 10 the

production of recombinant hEPO in host CHO cells and its recovery from the culture media. The specific CHO host cells used in the example are those designated as (DuX-B11) known in the art from a publication of Urlaub et al., the reference being given. The isolated product was found to be active both in vitro and in vivo (cf page 63, line 23 to page 64, line 15). On pages 64 and 65 the document reports the results of the preliminary characterisation of the CHO-produced hEPO. This includes a carbohydrate analysis in comparison with the urinary extract product according to known methods, which revealed the absence of fucose and N-acetylgalactosamine in both products and differences in the molar ratios of the other sugars. This leads to the conclusion that the recombinant hEPO produced had an average carbohydrate composition different from that of naturally-occurring erythropoietin (cf last sentence in Example 10).

23. In the light of document (1), the problem to be solved was the provision of a further method for producing biologically active recombinant hEPO.

24. As a solution thereto, claim 8 proposes a method characterised by the use of CHO cells which have the capability of producing N- **and** O-linked glycosylation, with incorporation of fucose and N-acetyl-galactosamine, **and** by the recovery and separation from the cells and the medium of a recombinant hEPO with N- **and** O-linked glycosylation.

25. The relevant question is whether the proposed solution would have readily occurred to the skilled person in order to solve the underlying technical problem.

26. In seeking an answer to the above question, account should be taken of the following:

(a) The results of the later scrutiny and verification of the carbohydrate constitution values reported in document (1) (cf the many declarations on file on this subject) were not available to the skilled person. Thus, the skilled person would have taken the disclosure in document (1) at its face value (cf also point 19, item b), last sentence supra);

(b) No prior art document was available indicating whether or not CHO cells perform under all circumstances N- **and** O-linked glycosylation, with incorporation of fucose and N-acetylgalactosamine. The respondents, who were specifically requested at the oral proceedings to produce such a prior art document, were unable to point to any document. The skilled person could expect the glycosylation machinery of eukaryotic cells, in particular of CHO cells, to carry out, depending of the experimental circumstances of a case (culture condition, structure of the core protein, tridimensional configuration etc.), either N- or O-linked glycosylation or both or none;

(c) No O-glycosylation had been detected in the urinary Epo (cf document (3)). The latter document stated that all of the oligosaccharides were N-linked in urinary Epo;

(d) Prior art document (4), which described transient expression of recombinant hEPO in COS cells stated that: "Whether any of the glycosylation is the

result of O-linked glycosylation is unknown" (cf page 809, right column, lines 10-11).

27. In the board's judgement, the skilled person, starting from the results reported in Example 10 of document (1), which at their face value pointed also in the case of recombinant hEPO to the lack of O-linked glycosylation, would **not** have readily thought of a method of producing hEPO in a recombinant system in which use was made specifically of CHO cells with the capability of producing N- **and** O-linked glycosylation, with incorporation of fucose and N-acetylgalactosamine, and in which specifically recombinant hEPO with N- **and** O-linked glycosylation was to be recovered and separated from the cells and the medium. In absence of any indication in the art of the essentiality or desirability of O-linked glycosylation in hEPO, the choice of such a way to operate has to be considered as non-obvious.

28. No different conclusion can be reached when the approach of respondents III is followed (cf Section XV, item b supra), ie when document (4) is taken as starting point and the problem to be solved is defined as the finding of a stable expression system for the production of recombinant hEPO. This is because, also when arguing along this path, no suggestion is found in the art as to the essentiality or desirability of ensuring that O-linked glycosylation takes place in the host cells in addition to N-glycosylation.

29. In the board's view, the apparently straightforward manner of operating which characterises the method of claims 8 and 9 can be derived from the available prior

art only with hindsight.

30. For these reasons, the subject-matter of claims 8 and 9 at issue involves an inventive step and consequently the main request is allowable under Article 56 EPC.

Sufficiency of disclosure (Article 83 EPC)

31. The respondents maintained that, if the board could not agree with their view that the disclosure of the patent in suit contained no more information than document (1), then it did not contain sufficient information that would lead a person of ordinary skill to the product indicated in claims 8 and 9. In particular, they objected that: **(i)** no methods, other than "conventional column chromatography methods", were indicated for the recovery of the recombinant hEPO of Example 11. In their view, this was important because the glycosylation pattern was also influenced by the purification process; **(ii)** it was not clear which of the cells referred to in Example 11 produced the recombinant hEPO which was analysed. These were most probably not the cells corresponding to the deposited clone also referred to in Example 10, but cells derived therefrom by additional cloning and selection work which was not described; **(iii)** the specific glycosylation pattern referred to in claim 9 could not be repeated, as shown eg by the authors of (E19) who in four different batches never obtained the same pattern.

32. The skilled person knew from document (1) how to produce recombinant hEPO in CHO cells. The knowledge added by the patent in suit is the indication to use CHO cells which have the capability of producing N- **and**

O-linked glycosylation, with incorporation of fucose and N-acetyl-galactosamine, and then to recover and separate from the cells and the medium recombinant hEPO with N- **and** O-linked glycosylation. These operations were well within the skill of the average person at the time of the invention as they required nothing else other than the application of known techniques of purification, testing and analysis. Under these circumstances, the board does not see any problem of insufficiency.

33. As regards the alleged lack of clear information in respect of the cells of Example 11, the board observes that it is true that Example 11 of the patent in suit refers to two different CHO cell lines of which only one, namely ATCC CRL8695, was made available by way of deposition. The plasmid used to transfect the other one was, however, also made available by way of deposition (ATCC 39989). Thus, one could indeed wonder whether the recombinant hEPO of Example 11 referred to in the specification and of which the sugar analysis is given (cf pages 11 and 12), was the product of the one or of the other. However, the most straightforward way for the respondents, who at first instance had the burden of proof (cf eg T 16/87, OJ EPO 1992, 212), to argue against sufficiency of disclosure, would have been to test at least the available CHO cell line and show that it did not express a recombinant hEPO with the features stated in claims 8 and 9 at issue. Such an approach was successfully used by the opposing parties, for example, in a case related to a deposited hybridoma secreting a monoclonal antibody with given functional characteristics which could not be confirmed (cf T 418/89, OJ EPO 1993, 20). After all, by rendering

publicly available at least one CHO cell line allegedly expressing recombinant hEPO according to the patent in suit and by stating that the said product purified by conventional chromatographic methods had the reported glycosylation pattern, the appellant provided a means for the verification of the veracity of their statements by third parties. If the latter (here: the respondents) have chosen not to take advantage of this possibility, this should not be a burden to the appellant. In this respect, the respondents did not discharge their onus of proof.

34. Thus, the board concludes that the respondents have not provided sufficient proof that the teaching of the patent in suit cannot be carried out by a person of ordinary skill on the basis of the description.

The adaptation of the description

35. The objections of the respondents to the proposed adaptation of pages 2 and 3 of the description were essentially that it did not sufficiently reflect the limitation of the method claims to N- and O-linked glycosylation by CHO cells.

36. In the board's judgement, it is not necessary to introduce amendments other than the ones proposed by the appellant, in particular in view of claim 1 to 7 of the main request (= claims 1 to 7 as granted) which are concerned with the recombinant DNA plasmid vector containing cDNA encoding human EPO of clone lambda HEPOFL13 and in general mammalian cells transformed therewith.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the appellant's main request, and the description and figures as requested by the appellant in the oral proceedings.

The Registrar: The Chairwoman:

U. Bultmann U. M. Kinkeldey