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D E C I S I O N
of 21 November 1994

Case Number: T 0412/93 - 3.3.4

Application Number: 84308654.7

Publication Number: 0148605

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Language of the proceedings: EN

Title of invention:
Production of erythropoietin

Patentee:
Kirin-Amgen, Inc.

Opponent:
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Merckle GmbH Chem.-pharm. Fabrik
Boehringer Mannheim GmbH Patentabteilung
Behringwerke Aktiengesellschaft
Akzo Pharma B.V.

Headword:
Erythropoietin/KIRIN-AMGEN

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123
EPC R. 28

Keyword:
"Circumstances where novelty of product by process features can be acknowledged"
"Sufficiency of disclosure of a dependent claim - no"
"Deposit not required by Rule 28 and Article 83 EPC to make something already possible easier; no best mode requirement under the EPC"
"Inventive step - yes"

Decisions cited:
T 0296/87, T 0205/83, T 0020/83, T 0181/82, T 0192/82, T 0877/90, T 0717/89, T 0069/83, T 0021/81, T 0281/86, T 0223/92, T 0301/87, T 0150/82, T 0130/90, T 0500/91, T 0418/89, T 0296/93

Catchword:
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Case Number: T 0412/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 21 November 1994

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office dated 20 January 1993 rejecting the opposition filed against European patent No. 0 148 605 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
S. C. Perryman

Summary of Facts and Submissions

I. European Patent No. 0 148 605 (application No. 84 308 654.7) was granted on the basis of 37 claims. The patent relates to the production of erythropoietin (hereafter: Epo; a list of all relevant acronyms used throughout this decision is to be found in Annex I).

II. Notices of opposition were filed by six opponents all requesting the revocation of the European patent on the grounds of Article 100(a) and (b) EPC. The objections under Articles 57 and 123(2) EPC raised by Opponent 01 have neither been substantiated nor followed up. During the procedure before the Opposition Division about four hundred documents designated P1 to P261e and P'154 to P'277 were relied upon by the parties. By a decision notified on 20 January 1993 the Opposition Division held that the patent as granted fulfilled the requirements of the EPC.

III. The Appellants, (Opponents 02 to 05) referred to hereafter as Appellants 02 to 05, respectively filed appeals against the decision of the Opposition Division with the payment of the fee, filed grounds for the appeals and submitted more than one hundred further documents (P262 to P365). Any citation among P1-P262e, P'154-P'277 and P262-P365, mentioned in the present decision can be found in Annex III.

IV. On 19 July 1994 and 25 August 1994 the Board issued two communications pursuant to Article 11(2) EPC of the rules of procedure of the Boards of Appeal with preliminary observations and comments on the case,

expressing doubts about the novelty and/or the inventive step of Claims 20 and 28 covering unglycosylated Epo over Dordall (P178b) possibly disclosing aglyco-Epo and about the inventive step of Claims 34 to 36 relating to the antibodies. The Respondents filed on 6 September 1994 a main request comprising Claims 1 to 31 no longer covering unglycosylated Epo and the antibodies.

V. Oral proceedings were held from 20 September 1994 to 23 September 1994. They were resumed on 21 November 1994 to announce the decision.

During the oral proceedings the respondents maintained the main request and filed auxiliary requests Nos. 1 to 15. The relevant claims of the Respondents' requests are to be found in Annex II.

VI. The written and oral submissions and evidence provided by the Appellants can be summarized as follows.

Sufficiency of disclosure (Art 83)

(a) The patent failed to fulfil the requirements of sufficiency of disclosure set out in Article 83 EPC. The Appellants argued and submitted experimental evidence to the effect that it would be impossible or at best it would require undue burden to re-isolate and express an Epo gene because no deposit of recombinant host cells was made and because of errors and omissions in the patent disclosure. During the Oral Proceedings, there was a concession by the Appellants that, (exception made for the cDNA coding for human Epo which was said not to be reproducible at all (see

Section (ah) *infra*)), the patent was enabling for all the claimed embodiments, however only within 4½ years (see Prof. Flohé's time table P339) which was an unacceptable burden. Sufficiency of disclosure required not only that an invention could be carried out at all but rather that this could be done without undue burden.

To buttress the above view, the Appellants emphasized the lack of reproducibility and/or the unacceptable burden required to carry out in relation to specific examples of the patent:

(aa) With regard to Example 4 relating to the screening of a Lawn gene bank with two oligonucleotide probes, the Appellants noted that the Lawn gene bank had not been deposited: its deposit with the depository ATCC happened later in 1985 (see P209, Section 3.1). However the identity of the deposited gene bank with the one of Example 4 was doubtful in view of the many amplification processes which could have fragmented or destroyed the Epo gene one is looking for. And indeed, Dr Grundmann's (P231, P252 and P253) as well as the firm Biopharm's (P209) Reports confirmed that repeatability of Example 4 was very time consuming if not impossible. According to Prof. Flohé (P339), it would have required 42 weeks for a team comprising a scientist and two technicians to carry out Example 4 if the gene bank had been available, while the burden would have risen to 66 weeks in the case that the gene bank had to be prepared specially.

(ab) With a view to Example 5 disclosing the characterization and sequencing of the positive clones,

the Appellants submitted that the errors or omissions affecting Table VI of the patent would have rendered impossible the identification by restriction enzyme mapping of the genes looked for, as also confirmed by the tests performed by Prof. Schaffner (P204 and P205). The above deficiencies would have required, according to Prof. Straus and Dr Moufang's Report (P316), sequencing again the positive clones and this operation represented an unacceptable burden. Furthermore, the Appellants pointed out that the above mentioned errors and omissions in Table VI affected the non coding region, in particular intron I, which comprised important regulating elements for the mRNA processing in the cell (see P333).

(ac) Examples 6 and 7A, disclosing the construction of vectors pDSVL1 and pSV4SEt, could not be reproduced by the person skilled in the art based on the information given. In particular, it was not taught which restriction enzymes should have been used to obtain region 2448-4362 from pBR322, nor how to obtain the 237 bp sequence of SV40, not to mention which linker should have been used (see the Reports of Prof. Gassen P208, p.8 and of Biopharm P209, Section 3.2). Construction of vectors equivalent to pDSVL1 and pSV4SEt would have required, according to Prof. Flohé (P339), 6 man x months. The DHFR minigene referred to in P38 was not available to the public either. Moreover, when trying to reproduce Example 7A with techniques and vectors available in 1992, Drs Schumacher and Kalusa (P210) did not obtain any expression. Dr Schumacher (P207) constructed plasmid pEPO303 comprising a purportedly aleatory sequence at positions 782-1166, corresponding to the sequence [I.S] of Table VI, ie, a portion of the

5' non coding region the Patentee failed to sequence. The fact that pEPO303 yielded neither Epo nor correct mRNA showed the criticality of the missing sequence for Epo expression.

(ad) Example 7B disclosed removal of a 5'-BstEII-BamHI-3' Epo gene fragment of 4.9 kb from plasmid pUC8-HuE and the insertion thereof, by means of a synthetic linker comprising SalI and BstEII sticky ends and an internal BamHI recognition site, into vector pBR322 previously cut with SalI and BamHI. The error in Table VI of the patent spanning exactly the BstEII restriction site, 44 bp 5'-upstream from the ATG start codon (GGTGACC should have been GGTCACC) would have prompted the skilled worker wishing to reproduce Example 7B to synthesize a wrong linker (GGAC---BamHI----SalI instead of GGAG---BamHI ---SalI). Once the above wrong linker was used (together with the Epo gene fragment and the open plasmid pBR322), no ligation product would have formed. Prof. Schaffner provided experimental evidence (P204, page 8) in this respect.

(ae) As to Example 10 relating to expression of Epo in COS-1 and CHO DHFR$^-$ cells, firstly it was pointed out that plasmid pDSVL-gHuEPO (with a wrong linker) of Example 7B has been used to transfect a CHO cell: therefore the objection raised against the vector was to be extended to the transfected CHO pSVgHuEPO cell. Neither the above cells, nor plasmids pMG2, pDSVL-MkE and pDSVL-gHuEPO were available to the public at the priority date of the patent (P208, page 10). The cell line CHO DHFR$^-$ was one that had undergone mutagenesis to yield sub-strain (DuX-B11) CHD K1 which had not been deposited. Since the glycosylation pattern of any Epo

expressed by a cell depended upon the cell itself, as Prof. Pamela Stanley confirmed in P215, it was doubtful whether the same glycosylation pattern could ever be obtained in the absence of the deposited sub-strain (see opinions of Prof. Haselbeck P213b, Dr Fritsch P216, Section 3.3, Prof. Straus and Dr Moufang P316 and Biopharm P209).

Moreover, as admitted by the Respondents, the carbohydrate analysis performed in Example 10 was erroneous. Therefore, the skilled worker repeating Example 10 would have found a discrepancy between the sugar content of his recombinant product and that of r-Epo reported in the Example, and thus would have discarded his Epo as discrepant from the one looked for (see declarations of Prof. Haselbeck (P213b) and Dr Fritsch (P216)). Finally, the amplification technique disclosed in Example 10 would have required an additional burden of about half a year.

(af) The repeatability of the synthetic gene fragments disclosed in Example 11 and their expression in *E.coli* as disclosed in Example 12, was also questionable in view of the unacceptable burden (2 years according to Prof. Rack, see P224) required to synthesize them and also because the synthetic DNA merely enabled the preparation of unglycosylated Epo, which was inactive not only owing to the absence of sugars, but also because Epo would have to be recovered from inclusion bodies of *E.coli* and it still needed to be renaturated (see Prof. Rudolf's expert opinion P212), not to mention the possibility (Prof. Gassen P208) that Epo might be degraded by proteases under the conditions shown in Example 12.

(ag) Prof. Straus and Dr Moufang therefore emphasized in their opinion (P316) that under these circumstances there was an obligation to facilitate the reproducibility by deposition of an r-Epo producing clone according to Rule 28 EPC.

(ah) The Appellants further denied that the patent was enabling for the cDNA coding for human Epo of Claim 3 at all. There were three possible methods for obtaining the cDNA coding for human Epo: (i) transfection of a COS-1 cell with a vector carrying the g-DNA coding for Epo, isolating and reverse transcribing the mRNA, as referred to in Example 5, last 3 lines of page 23 of the patent; (ii) starting from a cell sufficiently rich in mRNA and (iii) chemical/enzymatic synthesis. None of the above three methods could, at the priority date of the patent, yield any cDNA coding for human Epo.

(ai) Insofar as method (i) above was concerned, there was no literature showing that the above method had ever been used with success before. Wojchkowski (P281) rather than supporting the human cDNA's feasibility, refuted it, since the authors did not obtain a cDNA but rather a hybrid DNA containing part of the SV40 genome. The "Kurzgutachten" of Prof. Weissmann and Dr Menzl (P287) according to which human cDNA could be prepared in the light of the patent was contested, and counterarguments of Professors Hofschneider and Straus (P337a) and Prof. Zachau (P201) were provided.

(aj) Method (ii) was not available because no cell rich in Epo mRNA was known at the priority date of the patent. cDNA libraries were prepared only with difficulty thereafter as shown by P63 and P'183 (page 693,

paragraph bridging l.h and r.h columns) and by the Declarations of Dr Powell (P297), Dr Orkin (P280), Dr Davidson (P160) as well as P335.

(ak) The synthetic/enzymatic method (iii) for obtaining a cDNA, was not available because the synthetic genes disclosed by Examples 11 and 12 of the patent could not be named "cDNA". They lacked the leader sequence and therefore they were not even "ORFs". According to Prof. Gassen's Report (P336) nobody succeeded as of 1983 in preparing by chemical/enzymatic synthesis a cDNA coding for a glycoprotein to be expressed in a mammalian cell. The synthetic genes coding for interferon-α referred to in P'199, P'200, P292a and b had been expressed in *E.coli* where no glycosylation takes place. The technique for synthesis of long genes required alteration of the codons to facilitate their synthesis. Therefore, the obtained synthetic gene could not be termed "cDNA". Moreover, the above technique could not be applied in the synthesis of a gene of about 5,000 bp corresponding to the length of the cDNA coding for human EPO including the 5'/3' flanking sequences.

Novelty

(ba) Appellant (02) contended that the DNA sequence claims and dependent claims lacked novelty. The DNA claims and the claims to transformed cells/recombinant process were anticipated by the Lawn/Maniatis gene bank (P79) and by P125, respectively. Against the recombinant process and possibly the polypeptides, P111 was cited.

(bb) There was consensus among all the Appellants that the claims to the polypeptides lacked novelty. They argued

that there were no differences between the claimed r-Epo and the prior art u-Epo disclosed by Miyake (P89), Sasaki (P113) Yanagawa (P150), Sue (P121) and Egrie (P343) which were sufficient to establish novelty. It was possible by selection of the expression system and the purification process to imitate the natural product as closely as they liked. The product-by-process format of the respective claims was inadequate to distinguishing r-Epo from u-Epo, since it could not be seen as a reliable parameter in the sense of the finding in decisions T 296/87 (OJ EPO 1990, 195) and T 205/83 (OJ EPO 1985, 363), which would allow a distinction to be made between the claimed r-Epo and u-Epo of the prior art. Thus, the Respondents had not been able to show that r-Epo as a class exhibited an intrinsic difference which turned up for any member of the r-Epo class and which allowed the skilled worker to know whether he was faced with r-Epo or with prior art Epo. Dr Sytkowski (P178a, page 3, first paragraph) declared that, given an Epo preparation, it was impossible to establish whether it was u-Epo or r-Epo on the basis of the sugar composition. This led to the unacceptable consequence that a third party was prevented from knowing whether he acted outside or within the scope of Claim 20 of the patent. In the Product License Application (P276, pages 762 to 763) filed by the Respondents with the Food and Drug Administration (FDA) and P196 (Product Description of Erypo®, see Section 13.1), the Respondents declared that r-Epo from CHO cells was indistinguishable from u-Epo. Most relevant submissions for showing identity or refuting alleged differences between r-Epo and u-Epo in respect of the sugar composition, specific activity, IEF, SDS-PAGE, presence of NeuAcα(2→ 6)Gal linkages,

presence of sulphate or Neu5Gc/Neu5,9Ac_2 moieties, etc, were the following literature and/or Experts' opinions: Dr Conradt (P312 and P337b), Dr Fukuda (P318), Dr Jeffcoate (P330), Prof. Haselbeck (P331), Storring (P261c, page 473), Prof. Stanley (P215), Conradt (P317), Takeuchi (P261a), Sasaki (P114), Nimtz (P269) and Schauer (P332).

Inventive step.

(ca) The inventive step of the claims to DNA sequences and dependent claims, was challenged by three lines of arguments based on approaches A, B and C for isolating Epo DNA which already existed at the priority date of the patent and all of which would have reasonably expected to succeed by the skilled person in 1983. The approaches were the following:

A) The immunoprecipitation approach of Korman (P73): This approach consists of using an antibody against Epo in order to precipitate the polysomes, which are complexes comprising the mRNA, the ribosome and the nascent protein. Immunoprecipitation of the polysomes would have provided an enriched Epo mRNA source, departing from which it was within the skills of anybody to prepare the corresponding Epo cDNA by reverse transcription. Both an Epo producing cell line (Katsuoka, P70) and an antibody against Epo (Sue, P121) were available for carrying out the above technique.

B) The short probe approach of Seki (P116):

the above technique consisted of using two short degenerate oligonucleotides as probes, designed in the light of the 26 N-terminal amino acids of Epo as disclosed by Sue (P121), or in the light of further amino acid sequence data which could be achieved by further Epo sequencing. With the protein obtainable from Miyake (P89), it was within the skills of the general practitioner to prepare tryptic digests and to determine the partial amino acid sequence of such digests as shown by Dr Lottspeich's (P189) and Dr Por Lai's (P298, P299) Declarations and by Browne (P'183, page 694, l-h column, 1st paragraph). The Appellants maintained that the inventor's previous attempts were unsuccessful only because he did not have available sufficient amino acid sequence information. As soon as he was provided by Dr Lai with additional sequence information, he was successful within a few weeks. However, the skilled person was in a position to sequence the protein, had a sufficient quantity thereof been available. Amino acid sequence information was "the key to the kingdom" rather than the inventor's screening process, which already belonged to the prior art. It was further argued that the fact that Dr Powell succeeded in cloning the gene in 1985 using techniques and materials available in 1983 (see Dr Powell's Declarations P293 and P297) supported the view that there was no special hindrance in isolating the Epo gene. In line therewith was Dr Sytkowski's Declaration III (P295), according to which the National Institute of Health (NIH) support to Prof. Orkin at Harvard Medical School constituted evidence that success

in achieving Epo gene cloning was reasonably expected. In Dr Sytkowski's view, Prof. Orkin's project failed only because of the limited supplies of u-Epo.

C) The long probe approach: a technique was disclosed by Anderson (P3) and Jaye (P64) which substantially consisted of designing a long probe (guessmer) based on estimating the codons likely to be employed in the target gene (mammalian, human), then using said guessmer to pick up the gene. It was argued that it was possible to pick up the Epo gene with a long probe based on the 26 amino acids long N-terminal sequence of Epo available from Sue (P121). The above theoretical argument was buttressed with experimental tests carried out by Dr Grundmann (P231, P252 and P253), who successfully isolated the Epo gene with long DNA probes designed by Prof. Lathe (P180, P230 and P251). Dr Grundmann's first probe (P231 and P253) was a 81-mer designed by Prof. Lathe in the light of Anderson (P3) with the mammalian preference codons of Grantham (P50), whereas the second probe (see P252) only differed therefrom by the selection of human rather than mammalian preference codons from Grantham (P50). It was emphasized that the long probe approach was successful despite the errors affecting positions 7 and 24 of the Sue (P121) sequence.

(cb) Insofar as claims to the polypeptides were concerned, it was also denied that these involved an inventive step. They argued that since the Respondents maintained that r-Epo differed from u-Epo, the structural

difference should have led to a surprising and advantageous effect in accordance with what had been decided in comparable cases by decisions T 20/83 (OJ EPO 1983, 419), T 181/82 (OJ EPO 1984, 401) and T 192/82 (OJ EPO 1984, 415). However, the Respondents had not been able to demonstrate the superiority of r-Epo over u-Epo, since they admitted the equivalency thereof (Egrie (P343) and also PLA (P340, page 762)) from the viewpoint of both biological activity and immunological reactivity (pages 213 and 215). Nor could the Respondents rely on an alleged higher specific activity for his r-Epo, since the patent did not teach how to obtain said higher specific activity. They also relied on decision T 877/90 of 28 July 1992 (not published in the OJ EPO) for their attempt to show that r-Epo was a mere obvious *desideratum* and on decision T 717/89 of 25 March 1992 (not published in the OJ EPO) for stating that a beneficial effect, such as the greater quantity, following inevitably from a recombinant DNA process cannot justify the inventive step.

Appellants' expert Dr Sytkowski argued that it was reasonable to expect that the expression of the Epo DNA sequence in COS and CHO cells would have yielded r-Epo biologically active *in vivo* (P360) and provided a list of prior art documents (P125 and P360-7 to P360-22) dealing with *in vivo* active recombinant glycosylated proteins. Whether these were obligate glycoproteins or not, had no bearing on the inventive step issue.

On a different line of argument, the equivalence of the *in vivo* biological activity of r-Epo and u-Epo was addressed by stating that biologically active r-Epo was at the end of a one-way street which those seeking to

express the Epo gene were travelling. Therefore the biological activity was to be seen as a mere bonus effect that could not justify any inventive step in accordance to decisions T 69/83 (OJ EPO 1984, 357) and T 21/81 (OJ EPO 1983, 15).

VII. The Respondents argued essentially as follows:

Sufficiency of disclosure

(aa) The Respondents maintained that the patent disclosure could be practised by the skilled person without undue effort and expense. They provided their own time estimates. The Wojchowski paper (P281) supported this view because the experimental procedures described corresponded essentially to those of the Examples of the patent. Additional evidence of the sufficiency of disclosure was to be found in the submissions of the Appellants themselves (Grundmann's P231, P252 and P253). Further evidence was to be found in P164, page 1753, wherein it was stated by another company trying to succeed in expressing Epo in a recombinant system that they succeeded after the full sequence of the Epo gene had been published in P63, and in Prof. Orkin's Declaration (P280): "I would further add that once the Epo gene was cloned and the sequence made available, it was straightforward for someone to clone and express the Epo gene".

Referring to the Appellants' attack on non sufficient disclosure of specific examples, it was pointed out that these did not need to be exactly repeatable in view of Decision T 281/86 (OJ EPO 1989, 202) and that no deposit under Rule 28 EPC was required. Detailed

analysis was given as to why any errors or omissions in the examples did not amount to an undue burden. For further details reference is made to the file and to the Reasons (see points 63ff *infra*).

Prof. Orkin and Dr Powell succeeded in cloning the Epo gene from Lawn library's (P79) equivalents within a period of a few months. The Declarations of Prof. Orkin (P280, Section 16) and Dr Sytkowski (P289, Sections 7 to 14) both focusing on the later publication P281 (Wojchowski), are in line therewith. As regards the time needed for preparing a library from scratch, Professor Murray stated during oral proceedings that in his laboratory the preparation of a library from a human hepatoma cell line to screen for hepatitis B sequences required about 4 to 6 weeks.

(ab) In reply to the objections that the patent was not enabling for a cDNA coding for human Epo, the Respondents provided their own definition of the term "cDNA" as an ORF devoid of introns. Further it was relied on the finding in Decision T 223/92 HIF-γ of 20 July 1993 (not published in the OJ EPO) wherein the Board already expressed an opinion that a DNA sequence provided in a patent was an important piece of information for a sufficiently enabling disclosure. The letter from Genetics Institute to Chugai comprising a statement by Dr Fritsch (P 167, page 3), Prof. Lathe (P286) and Prof. Weissmann's Affidavit (P287), all supported the feasibility of the cDNA in the light of Table VI of the patent. Reference was also made to the later Integrated Genetics patent EP-A-0 267 678 with a view to demonstrating that a synthetic DNA comprising a reverse transcript linked to a synthetic fragment still

fulfilled the requirements of a cDNA's definition. It was also maintained that the synthetic genes "ECEPO" and "SCEPO" disclosed in Examples 11 and 12 were cDNAs. It was true, that these genes were susceptible of expression only in *E.coli* or in *S. cerevisia* and thus they were not properly glycosylated to ensure *in vivo* activity, however, the Examples served as a basis for the preparation of cDNAs suited to the expression in mammalian cells. The possibility of preparing the cDNA even in the absence of an enriched mRNA, by transfecting mammalian cells with a vector comprising the g-DNA and reverse transcribing the mRNA was mentioned in the specification of the patent and was a technique foretold by Prof. Weissmann (P287) and Anderson (P3, last paragraph).

Novelty

(ba) As regards the alleged lack of novelty of the claims hinging upon the DNAs over the Lawn's gene bank and Sugimoto (P125), reference was made to decision T 301/87 (OJ EPO 1990, 335) according to which a gene library did not anticipate an isolated nucleotide sequence comprised in said library.

(bb) Sugimoto (P125), unlike the invention in dispute, related to a cell fusion process involving no purified exogenous DNA. Regarding the novelty of polypeptides, it was made clear that none of the Appellants had been able to provide data about the true nature of the product secreted by the Sugimoto's (P125) cells, and, moreover, there were doubts about the enabling character of P125.

(bc) Comparative tests were provided to demonstrate that r-Epo differed from u-Epo of Miyake (P89) and that the Epo-A of Storring (P261c) was different from r-Epo, and corresponded to the prior art u-Epo of Sasaki (P113) and Yanagawa (P150). In addition a series of studies of r-Epo *versus* u-Epo reported in the literature showed differences in the carbohydrate portion. As an expert, Prof. Cummings (P262) summarized the 10 main differences between r-Epo and u-Epo.

(bd) The Respondents also held the product-by-process format as appropriate and cited decision T 150/82 (OJ EPO 1984, 309) and T 130/90 of 28 February 1991 (not published in the OJ EPO) in support of his contention.

Inventive step

(ca) The person skilled in the art would not have had a reasonable expectation of success when applying any of the proposed strategies A, B and C (referred to in Section VI (ca) *supra*).

In connection with the immunoprecipitation method (A), the Respondents drew attention to Prof. Wall's Declaration (P155, Section 19), according to which there had been neither a proper cell source for human EPO mRNA, nor a proper antibody.

With a view to the degenerate mixed short probe approach (B), it was emphasized that the attempt of Seki (P116) to isolate the DRα gene from a genomic library using degenerate mixed probes was a failure (see also Declaration of Prof. Silver (P157)), owing to the presence of an intron (see Korman (P174)). Because

of this knowledge of failure there could not have been a reasonable expectation of success. Reliance was also made on a statement in Anderson (P3, page 6838) to the effect that use of mixed oligonucleotide probes were impractical for screening genomic libraries.

As regards the long probe approach (C), it was disputed that the disclosures of Jaye (P64) and Anderson (P3) would have conferred on the skilled person any basis for confidence in cloning an Epo gene as confirmed by Prof. Davidson's Declaration (P160, Sections 23, 24 and 25). The skilled person would not have combined Jaye (P64) and Anderson (P3) with Sue (P121) because the N-terminal sequence provided by the latter document comprised a high number of codons with a 6-fold-degeneracy and Jaye and Anderson taught that such highly degenerate sequences should be avoided, or would not have held it as a viable approach after having thoroughly considered all the points below.

- Jaye's and Anderson's long probes are designed in the light of the full length known amino acid sequence of factor IX and BPTI, respectively, while no such information was available for Epo.

- Jaye and Anderson were able to chose areas of least degeneracy, while no such regions were available from the published sequence of Sue.

- Jaye used the codon usage found in sequenced cDNAs of bovine proteins secreted by the liver. In the light of this, the probe should have been based on the human codon usage of kidney, which was not known.

- Jaye and Anderson were able to characterize the putative positive clones by reference to the known amino acid sequences of factor IX and BPTI, while it was not so in the case of Epo.

- the Anderson's 66-mer probe was not specific and moreover they merely picked up an exon.

Dr Grundmann's successful probes had been designed by Prof. Lathe with information not available to the skilled person in 1983, ie, the following information became available to the skilled person only after the patent publication:

- the Grantham tables (P50) had enough correlation to the Epo codon preference

- despite Epo being a rare protein there were no underlying unusual codons

- the full Epo gene was present in a Lawn (P79) genomic library

- a long probe based anywhere in position 1 to 26 of the Sue sequence did not span an intron.

- there were only two mistakes in the Sue's sequence

The hybridization conditions used by Dr Grundmann when he performed his experiments with the long probes (see Prof. Davidson's Declaration (P160, Sections 28 to 32) were also questionable.

The Appellants' withdrawal of reliance on Jaye (P64), once Prof. Davidson highlighted that the Jaye's instructions were partially incorrect (see P160, Sections 19 and 31) left unanswered the question of how the skilled person would have reconciled the different probe design instructions of Jaye and Anderson. The skilled person would have taken the long probe approach *in toto*, without setting aside the teachings of Jaye (P64) and focusing only on the Anderson paper (P3), as the Appellants did when carrying out their experiments.

The Respondents also provided during the oral proceedings an analysis of "Prof. Lathe's List", namely a list of 19 examples of application of the long probe approach after the priority date of the patent [P24, P133, P131, P134, P102, P130, P146, P25, P85, P26, P78, P10, P72, P5, P1 (2 examples), P132, P52 and P12], from which it turned out that nobody actually used the Anderson's approach as such. As a further criticism of the long probe approach, it was outlined that Dr Fritsch, who was looking for the Epo gene, did not turn to this new technique despite years of failure.

(cb) In support of the inventive step of the polypeptides, the emphasis was placed on the problem the patent aimed to overcome, namely to provide polypeptides which had the *in vivo* biological activity of naturally occurring Epo and that the solution to that problem was the provision of these polypeptides. The claims were neither claims to more or more purified Epo, nor claims to Epo with improved properties. Therefore, none of the decisions cited by the Appellants relating to products with better properties, "obvious *desideratum*", etc, applied here. The inventive step of the proteins

followed from the fact that it was truly remarkable that despite the differences due to the recombinant DNA process, one got an obligate glycoprotein that has *in vivo* biological activity devoid of adverse immunological properties. In support of the above view, attention was drawn to decisions T 130/90 (*loc. cit.*) where a similar situation had been dealt with. It could not be known in advance that a new polypeptide never produced before would be effective when even the natural product was not completely characterized. That r-Epo exhibited the properties of u-Epo did not follow plainly and logically from the prior art for the two reasons that there was no reasonable expectation that a product of eucaryotic expression would have exhibited the *in vivo* biological and immunological properties of the natural obligate sialoglycoprotein u-Epo and that even when viewed as a *desideratum*, *desiderata* are not unpatentable by virtue of decision T 500/91 of 21 October 1992 (not published in the OJ EPO).
Dr Sytkowski's arguments that it was known that eucaryotic cells could properly glycosylate Epo to ensure the *in vivo* biological activity thereof, were refuted with the provision at the oral proceedings of Figure D (page 929 of the Appeal file), i.e., a list of Dr Sytkowski's Exhibits, wherefrom it transpired that only human t-PA of documents P360-20a and P360-20b was an obligate glycoprotein. However, it was only in late 1984 (see P283), i.e., after the patent's priority date that t-PA turned out to be an obligate glycoprotein, therefore it was impossible to predict whether by expressing an obligate glycoprotein in an eucaryotic cell, one would have any *in vivo* activity at all.
Prof. Cummings submitted at the oral proceedings how

complex and poorly understood were the COS and CHO cells' glycosylation and sialation mechanisms.

VIII. *Requests*

The Appellants (Opponents) requested that the decision under appeal be set aside and that the European Patent No. 0 148 605 be revoked.

The Respondents (Patentee) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or one of the first to fifteenth auxiliary requests respectively, all as submitted at the oral proceedings on 22 September 1994, and a description to be adapted if necessary.

Reasons for the Decision

1. The appeals are admissible.

Preliminary comments

2. The length of this decision and some unusual aspects of these proceedings make preliminary comments appropriate, and in particular an indication of matters on which there was no dispute.

3. Firstly, it was not in dispute that the European application as filed, in relation to all matters of importance to this decision, was entitled to the priority of the US priority document of 13 December 1983. So this is the only date of significance for judging whether something could be regarded as prior

art or not. Thus in this decision "prior art" refers to documents made available to the public before the priority date of 13 December 1983.

4. Secondly the parties agreed that for this case the skilled person should be treated as a team of three composed of one PhD. researcher with several years experience in the aspect of gene technology or biochemistry under consideration, assisted by two laboratory technicians fully acquainted with the known techniques relevant to that aspect. This applied equally whether the question under consideration was obviousness for the purpose of Article 56 EPC or sufficiency for the purpose of Article 83 EPC. For different aspects the composition of the team might vary depending on the knowledge and skills required by that particular aspect. This definition of the skilled person coincides with the view of the Board, and references in this decision to "skilled person" are to be interpreted as meaning this team. In decision T 223/92 (*loc. cit.*) where the priority claimed was for much the same time, 1983, as in this case, the Board considering that case defined the "skilled person" as a highly skilled technician (see point 5.5 of reasons), which in real terms would mean a PhD. researcher for the knowledge. The notional skilled person in terms of patent law can then be treated as comprising this researcher and two laboratory assistants having the necessary manual dexterity and lack of fatigue.

5. All the written submissions and documents before the first instance and those filed on appeal in due time remain matter to be considered by the Board, whether or not there are oral proceedings before the Board, unless

all parties should agree that such earlier submissions are no longer relied on and can be disregarded by the Board. There was no indication at the oral proceedings of any agreement between the parties that any earlier documents or submissions need no longer be considered: on the contrary, many apparently short statements at the oral proceedings referred to earlier statements which in turn referred to numerous documents. While the Board assumes that the most important aspects of each party's case will have been presented at the oral proceedings, the task remains of assessing the case presented at the oral proceedings in the light of all the written and oral submissions.

6. During the course of the opposition and on appeal, apart from voluminous submissions by the parties' representatives, more than five hundred documents were filed. These included not only prior published documents and statements made specifically for the purpose of these opposition and appeal proceedings, but excerpts from statements, expert opinions, and judgements in more than twenty other proceedings in various patent offices and national courts around the world, involving the parties to this appeal and/or their respective licensors and licensees in various combinations, such proceedings relating to the present patent, its equivalents in other countries and other patents relating to Epo, some of them owned by the Appellants or their licensors. All the latter type of documents are likely to involve delay in the issuance of a decision. This is because the Board needs to consider not only the statements contained therein, but to assess whether the context of the statements is sufficiently clear, either in itself or from other

evidence, for the statements to be treated as being reliable and relevant to the issues in these proceedings.

7. In particular the differences between the issues relevant in EPO proceedings and the issues relevant in US patent law, whose concepts such as first to conceive, first to reduce to practice, disclosure of best mode, and importance of an application being filed in the name of all the inventors, have no equivalent in European patent law mean that isolated statements from US proceedings can be highly misleading, whereas complete consideration of the material would overwhelm the proceedings with matters not relevant to the issues relevant here, namely what does the patent specification and the prior art say, and what, within his capabilities on the basis of common general knowledge, do these teach the skilled person to do as of 13 December 1983.

8. Under Article 60(3) EPC, for the purposes of proceedings before the European Patent Office, the Applicant shall be deemed to be entitled to exercise the right to the European patent. Under this Article the inventor shall have the right, *vis-à-vis* the Applicant for or a proprietor of a European patent to be mentioned as such before the European Patent Office. If there is any dispute as to inventorship or entitlement to the patent, the European Patent Office has no jurisdiction to consider this, but this is a matter for the relevant national court to be determined in accordance with "The Protocol on Jurisdiction and the recognition of decisions in respect of the right to the grant of a European Patent" (Protocol on

Recognition). E.g., naming of the wrong inventor or non-entitlement to the patent is not a matter that the Board can consider in opposition proceedings.

9. The jurisdiction of the Board in these appeal proceedings is limited to the issues which can be considered on the oppositions that were filed, so the Board will refrain from commenting on issues which do not arise fairly on the present oppositions but are in dispute in other proceedings.

10. The discussion in respect of the requests considered to be unallowable, will be confined to the first issue that arises on the claims of that request considered in numerical order, in respect of which the Board considers that the requirements of the EPC are not met. Reasons for any claims being regarded as allowable, despite the arguments of the Appellants to the contrary, will only be given in relation to the request on which the Board sees no objections to any of the claims.

Main request

Sufficiency of disclosure (Article 83, EPC)

11. The Appellants are relying on two different lines of argument to deny sufficiency of the disclosure. Firstly while conceding that the skilled person using only his common general knowledge and the information contained in the patent specification would arrive at something falling within Claim 1, they argue that the time he would need to do so amounted to undue burden so that the invention is not disclosed in a manner sufficiently

clear and complete for it to be carried out by a person skilled in the art in the absence of a deposition of a suitable microorganism pursuant to Rule 28 EPC. Secondly they argue that in view of Claim 3 human cDNA coding for Epo, is part of the invention claimed, but that this has a precise meaning, and that relying on the information in the patent and the knowledge in the art at the priority date, the skilled person would be unable to make this however much time he was allowed. The second line of argument is an attack on validity quite distinct from the first line, so it can be dealt with separately even though both relate to sufficiency.

12. The Board thus has to decide what in the context of this patent specification Claim 3 directed to "A cDNA sequence according to Claim 1 or 2" covers, whether this includes human cDNA in the precise sense attributed to it by the Appellants, and if so whether or not the patent specification contains adequate instructions to enable the skilled man to make this.

13. Claim 3 of the above requests is directed to a cDNA coding for Epo. Since claim 3 depends on claim 2 directed to DNAs encoding human Epo, Claim 3 when dependant on Claim 2 must as a matter of construction cover a cDNA coding for human Epo.

14. The parties' arguments mainly focused on the definition of the term "cDNA". It is not disputed that the traditional meaning of cDNA is "a single-stranded DNA complementary to a messenger RNA ("mRNA") synthesized from it by reverse transcription, in vitro".

15. According to the Respondents' experts, the meaning of the above term has been expanded from this original meaning to also cover any natural or synthetic DNA sequence devoid of introns and coding for a protein, such as the "ECEPO" and "SCEPO" genes of Example 11. However this submission is inconsistent with the terminology used by the Respondents themselves in the patent. The "ECEPO" and "SCEPO" genes of Example 11 are in fact termed "synthetic genes" rather than cDNAs.

16. There is no definition of cDNA as such in the specification. However at page 4 line 11 there is a reference to the "*in vitro* synthesis of a double-stranded DNA sequence by enzymatic "reverse transcription" of mRNA isolated from donor cells. The last-mentioned methods which involve formation of a DNA "complement" of mRNA are generally referred to as "cDNA" methods." In connection with Example 3 relating to monkey cDNA, a method is described of obtaining cells producing mRNA with an enriched production of the particular mRNA coding for the production of monkey Epo, and synthesizing a cDNA library from this by reverse transcription of all the mRNAs so produced, from which library the particular cDNA coding for monkey Epo is then isolated. The usage of cDNA here is in accordance with the traditional meaning of cDNA, and refers to a product obtainable by a particular process.

17. Only at page 23 line is there a reference to cDNA in connection with the human polypeptide sequence. It is stated: "Presence of the lysine residue in the human polypeptide sequence was further verified by sequencing of a cDNA human sequence clone prepared from mRNA isolated from COS-1 cells transformed with the human

genomic DNA in Example 7, *infra*." This reference is again consistent with the traditional definition of cDNA, and in no way suggests the extended meaning suggested by the Respondents.

18. The Appellants' experts submitted that a cDNA should be a true copy of the messenger RNA (mRNA) and also comprise 5' and 3' flanking sequences (eg. Prof. Zachau P201). Professors Hofschneider and Straus define a cDNA as an ORF, together with at least one flanking sequence comprising regulatory elements (P337a, page 34, lines 1 to 3).

19. The Board comes to the conclusion that as in the context of the description the term cDNA, in accordance with usual scientific usage, refers to the product obtained by *in vitro* synthesis of a double-stranded DNA sequence by enzymatic "reverse transcription" of mRNA, the reference to cDNA in Claim 3 must be interpreted in the same way. The unusual definition argued for by the Respondents is not consistent with what is said in the specification.

20. Thus Claim 3 when dependant on Claim 2 must be construed as being directed to a cDNA having a sequence equivalent to that obtained by reverse transcription from mRNA obtained from human donor cells, or possibly from recombinant cells producing human Epo. Whether this product claim can stand for the purposes of Article 83 depends on whether what is claimed can be identified, and whether a reliable method existed for making it using the teaching of the patent and common general knowledge available at the priority. For a cDNA the identification need not consist in a definition of

the base sequence, provided either explicitly or implicitly a method for making the cDNA is made available by the patent application.

21. The Board cannot agree to the Respondents' submission that Table VI of the patent implicitly discloses the cDNA. The table gives no information where the cDNA is supposed to start and stop. There is thus no unambiguous identification of any sequence in the patent as human cDNA. Thus the question to be answered is whether a reliable method of obtaining a mRNA as a source for a cDNA is disclosed or was common general knowledge.

22. It has now to be examined whether one of methods (i), (ii) or (iii) referred to in Section VI(ah) *supra* can be considered as such a method making possible to prepare the cDNA. There is agreement (see point 27. *infra*) that one barrier to making Epo by recombinant methods was that at the priority date there was no known source for obtaining mRNA coding for human Epo in a way which would enable a cDNA to be obtained from it. So the question of obtaining mRNA comes down to a question of whether the specification contains sufficient instructions for this.

23. As regards method (i), the parties provided contradictory evidence as to the feasibility of the method, referred to at the end of Example 5 of the patent, of making a cDNA human sequence clone from mRNA isolated from COS-1 cells transformed with the human gene coding for Epo, derived from genomic DNA. No details of this method are given in the patent. Example 7 referred to in Example 5 is quite silent

about obtaining mRNA. It is by no means clear that this reference in Example 5 indicates a complete cDNA sequence. As one of the Appellants' experts, Dr Fritsch, pointed out at the oral proceedings, that putative mRNA splice junctions in the human genomic sequence have been identified from the monkey cDNA sequence, would suggest that the full human cDNA was not available. This is because if a full human cDNA sequence had been available one would have expected this to have been used as this would have been a much more reliable way for identifying mRNA splice junctions than a comparison to monkey cDNA as there is no guarantee that there are no critical differences in the splice junctions for monkey mRNA and human mRNA. Further, if a full human sequence for human cDNA had already been available, the reader would have expected to see it given: its absence suggests that there may be problems in obtaining it. There is no prior art document suggesting that COS cells be used to obtain a mRNA. As Dr Fritsch, a co-author of the standard reference work for recombinant techniques ("Maniatis"), an extract of which is P171 published in 1982, also pointed out not only was such a method not in the 1982 edition, but not even in the 1989 edition is such a possibility referred to, making it extremely unlikely that at the priority date it could in any way be regarded as routine. Prof. Maniatis (P325) stated that the method used in Example 5 for obtaining a cDNA was highly questionable since it was not straightforward (mainly because of incorrect or alternate splicing) to obtain a correct cDNA by expressing a genomic clone in mammalian cells, isolating and reverse transcribing the mRNA. Dr Fritsch pointed out during the oral proceedings that COS cells very frequently mis-spliced

messages and that the Respondents did not make credible that the cDNA referred to in Example 5 of the patent was a full-length one. To his knowledge nobody had ever obtained a full-length cDNA from transfected COS cells. The Board considers that here the burden of proof is on the Respondents to show that the common general knowledge in the art would have enabled the skilled person to obtain a mRNA at the priority date given only the extremely scant information in the patent.

24. The Respondents rely on the statement of Prof. Orkin (P280) referring to events in 1985 as suggesting that a COS cell route to a mRNA coding for human Epo was feasible. This work in 1985 appears to the Board no safe guide as to what could have been done at the priority date. Further the work referred to appears to be related to the same work referred to in the Wojchowski paper (P281) of which Prof. Orkin was a co-author. This paper shows that in the experimental set up used with a SV40 vector, a "read through" of the ribonuclease results in a hybrid DNA comprising a portion of the SV40 genome, thus containing DNA stretches not belonging to the desired cDNA. The ribonuclease "read through" can be corrected only after going through a cumbersome series of operations involving a great many digestion and re-ligation steps (see Figure 1 and page 228, left hand column, bottom) aiming at replacing DNA derived from the vector SV40 and still containing parts of its DNA, with the 3'-terminus of the g-DNA coding for Epo. That it would always be possible to further process an incorrect cDNA to a correct one, as done in document P281, should not, in the Board's opinion, be taken for granted. The skilled person might be confronted with unexpected and

yet to be solved problems. These are not steps that the Board thinks it would be reasonable for a skilled person to take when trying to obtain a product not identified in the patent, which could amount to performing a further invention.

25. The Respondents also cite the last paragraph of the Anderson (P3) paper and the expertise prepared by Prof. Weissmann (P287) for the Swiss court as confirming the feasibility of the above approach (i). However, document P3 and Prof. Weissmann's expertise are found by the Board to confirm the theoretical possibility of using the above method (i) for preparing the cDNA, without being evidence that no experimental guidance is needed by the skilled person to carry this out at the priority date.

26. The Appellants rely on an Affidavit (P325) that Prof. Maniatis presented before the US court for arguing that expression in COS cells of the g-DNA and reverse transcription of the mRNA is not suited to obtaining the correct cDNA. The above Affidavit comprises experimental evidence represented by the Genentech's European patent application (see last page of P325) that a genomic sequence inserted into COS cell is incorrectly spliced, excising an exon. Dr Fritsch at oral proceedings agreed that this would be the case. This is also consistent with what the above mentioned Wojchowski paper (P281) states. This provides further confirmation for the view that the Board has come to, namely that no process is disclosed in the patent for making a mRNA from which a cDNA coding for human Epo could be made or identified. Method (i) could yield a human cDNA only in the instance the skilled worker were

lucky enough to pick up the full-length cDNA and this possibility is very remote in view of the experimental evidence provided by the Appellants. Should the skilled worker, though, pick up a defective cDNA as it is more likely, the task of turning it into a complete cDNA susceptible of expression in mammalian cells would possibly require a further invention.

27. As regards the approach (ii) (see Section VI(ah) *supra*) consisting of starting from a source rich in Epo mRNA, namely a cell wherein a significant portion of total protein synthesis is devoted to Epo, the Board notes an agreement between the parties, albeit in the context of the inventive step question, that no such enriched mRNA source was available at the priority date of the patent (see the Respondents' submission of 25 February 1992, pages 12 to 14; Browne (P'183, paragraph bridging left hand and right hand column of page 693); the Declaration of Prof. Wall (P155, Sections 18 and 19); Dr Hirt (P202, bottom of page 2) and Prof. Schaffner (P205, item 6) for the Appellants). Some Appellants relied, when arguing on inventive step (Article 56 EPC), upon the Farber abstract (P32) as disclosing an alleged enriched Epo messenger source, but failed to show that it would have been possible to isolate mRNA relating to Epo from this in a way that would have enabled the skilled person to revert it into cDNA. This method (ii) thus cannot be regarded as feasible.

28. As for method (iii), i.e., complete synthesis of the cDNA, this would require the skilled person first to know what he had to synthesize, and secondly to have a practical method of synthesizing it. To identify a partial sequence in Table VI as being the cDNA would be

mere guesswork. Neither is there an unambiguous information of the start nor an indication of where the end should be. Thus the skilled person would be unable to use this approach. In these circumstances it is not necessary for the Board to consider in relation to this Claim 3, whether the skilled person could have synthesized a sequence which was later identified as the cDNA, given only the information in the patent and common general knowledge at the priority date.

29. Consequently, Claim 3 of the main request does not comply with Article 83, EPC, so that the main request is not allowable.

Auxiliary request 1

30. Auxiliary request 1 contains as Claim 3 a claim with identical wording to unallowable (see paragraphs 1 to 29 *supra*) Claim 3 of the main request. Therefore auxiliary request 1 is not allowable.

Auxiliary request 2 - allowability of amendments and novelty of Claim 19

31. This request does not contain unallowable Claim 3 and has, therefore, to be examined whether any other claim contravenes a requirement of the EPC. Claim 19 differs from Claim 20 as granted only by the insertion of the word "recombinant" before "polypeptide" in line 1, and by the deletion of the words "procaryotic or" in the reference to "characterized by being the product of procaryotic or eucaryotic expression of an exogenous DNA sequence" at the end of the claim as granted (this was the restriction made by granted dependent

Claim 21). The deletion of this alternative restricts the scope of the claim. The insertion of "recombinant" is an anticipatory reference to the feature "characterized by being the product of eucaryotic expression of an exogenous DNA sequence" at the end of the claim, and does not extend the subject-matter beyond the original disclosure or the scope of protection of the claims or make it any less clear. There are thus no objections to this amended claim on the basis of Articles 84 or 123 EPC.

32. The prior art includes u-Epo with a specific activity of 70,000 U/mg disclosed by Miyake (P89), comprising Epo-α and Epo-ß, and u-Epo with a specific activity of 81,600 U/mg disclosed by Sasaki (P113), obtained by a process involving a monoclonal antibody. This is admitted to form part of the prior art by the Respondents. The only feature on which a distinction between Claim 19 and this can be based is the feature "characterized by being the product of eucaryotic expression of an exogenous DNA sequence" and the definition as a "recombinant protein".

33. As has already been explained in other EPO Board of Appeal decisions (cf. T 150/82, *loc. cit.*, and T 205/83 *loc. cit.*), and as was emphasized by the Board during the oral proceedings in this case, the fact that a product is referred to in a claim as being the result of some process, does not automatically mean that the product is novel even if it is beyond dispute that the process referred to is new. The purpose of the reference to the process was to exclude those products which in the prior art were not obtained by the process. If, on the evidence available, the process

appears capable of producing every product meeting the characteristics of the product of the prior art, the reference to the process is not a limitation for the purpose of considering novelty. The process feature in a product claim can only be relied on for establishing novelty over the prior art, where use of that process necessarily means that the product has a particular characteristic and the skilled person following the teaching of the specification would inevitably achieve that characteristic, would be aware of that characteristic and would discard any products not having it. This is not the case here.

34. In the text of the patent as originally filed, what information there is comparing the recombinant Epo with urinary Epo, is to be found on page 29 lines 6 to 30. Of this what is stated at lines 17 to 26 is admitted by the Respondents to be wrong and unreliable, as it was based on an analysis which went wrong in some unspecified way. This leaves lines 6 to 16, based on a different analysis, which the Respondents still rely on and which has not been shown to be wrong, stating that recombinant Epo produced from COS-1 and CHO cell expression had a higher molecular weight than u-Epo, and the general statement at lines 27 to 30 of page 29: "Glycoprotein products provided by the present invention are thus comprehensive of products having a primary structural conformation sufficiently duplicative of that of a naturally occurring erythropoietin to allow possession of one or more of the biological properties thereof and having an average carbon composition which differs from that of naturally-occurring erythropoietin."

35. The Board does not interpret this statement as an exclusion from the "Glycoprotein products provided by the present invention" of products that are close to u-Epo available in the prior art, nor as giving the skilled person any instruction or reason for avoiding something as close to u-Epo as can be achieved. The use of the term "comprehensive" suggests merely that products different from u-Epo can be obtained, not that there is any recognizable advantage in doing so. The property of interest in Epo is the carbohydrate composition only insofar as its biological activity is concerned, and the specification gives no information from which it can be deduced that differences from u-Epo are in any way desirable for biological utility.

36. According to the Respondents, every study reported in the post-published literature demonstrated that r-Epo differs "significantly" from u-Epo in the carbohydrate portion of the glycoprotein. These differences are supposed to be found consistently between any r-Epo produced in a variety of host cells and the u-Epo preparations of the prior art. The Respondents pointed to the ten differences stated to exist between r-Epo and u-Epo in the recapitulative Table on page 20 of Cummings (P262) which are the following:

- Differences in apparent m.w on SDS-PAGE : see the patent, page 29, lines 6 to 16, Yanagi (P268a, page 422), Sasaki (P114, page 12061), Imai (P268b, page 354)

- u-Epo is more acidic on IEF: see Storring (P261c, pages 473 and 474), Dr Strickland's Declaration (P228, page 5), Wide (P261e, page 126)

- Differences in the oligosaccharides by HPLC: see Yanagi(P268a, page 424), Sasaki (P114, pages 12063 and 12070), Dr Strickland's Declaration (P228)

- Differences in the linkages within the oligosaccharide chains: see Takeuchi (P261a, page 3657), Nimtz (P269, page 39)

- Higher percentage of extensions/repeating structures within the sugar chains for r-Epo: see Tsuda (P266, page 5659), Takeuchi (P261a, page 3659), Sasaki (P114, pages 12064 to 12067)

- Different isoform distribution for N-linked chains for r-Epo in comparison with u-Epo: see Tsuda (P266, page 5649), Takeuchi (P261a, page 3659)

- Higher number of sialic acids in r-EPO: see Sasaki (P114, pages 12059 and 12070), Nimtz (P269, page 54).

- More highly branched oligosaccharides in r-Epo: see Tsuda (P266, page 5649), Takeuchi (P261a, page 3659)

- Higher specific activity for r-Epo: see Imai (P268b, page 356), Storring (P261c, page 476)

- Higher percentage of sulphated oligosaccharides in u-Epo: see Dr Strickland's Declaration (P228).

37. However, study of these documents reveals that these differences can be attributed only to the particular cases under investigation and cannot be generalized to

r-Epo as a class. For instance, the Respondents' assumption that r-Epo will always exhibit a higher number of sialic acids is contradicted by Goto (P47, Table 3), which shows that r-Epo-ψ from ψ-2 cells comprises only 5.0 moles/mole Epo of sialic acid (NeuNAc), while u-Epo has 10.7 moles/mole. The above statement about the sialic acids is also questionable in view of the fact that the claims are not limited to a particular purification process, which purification process plays a fundamental role on the sialic acid content (presence or absence of neuraminidase inhibitors, pH of the buffers, etc.).

38. As regards the molecular weight by SDS-PAGE, Figure 2 of Goto (P47) shows that r-Epo-ψ exhibit a lower molecular weight by SDS-PAGE than u-Epo, contrary to the Respondents' contention. With a view to the specific activity, which the Respondents maintain to be always higher for r-Epo, the parties have not disputed that this parameter is again linked to the purification process rather than to intrinsic properties of r-Epo. Further and importantly this is a parameter which is not mentioned in the claims. The Respondents' statement that r-Epo will have a more highly branched oligosaccharide portion than u-Epo, is contradicted by the Wojchowski article (P281, page 229, right hand column, lines 17 to 18) disclosing r-Epo with truncated oligosaccharide chains. Likewise, the generalization of other differences serving as distinguishing features inherent in the whole class of r-Epo, do not convince the Board. The Respondents have not been able to demonstrate that any one of the above 10 distinguishing features for r-Epo is a "universal" one for the whole class of r-Epo. The Board has thus to consider these

differences as not reliable. In fact, while the r-Epo glycosylation pattern mainly depends on both the expression system and the purification process, the differences outlined by the Respondents occur randomly, without their being reliably predictable on the basis of the information in the patent specification. Random variation is indeed supported by Table I of Sasaki (P114, page 12061) showing substantial variations of the r-Epo carbohydrate composition even within 4 batches obtained from the **same** expression and purification system. For instance, r-Epo of Batch 1 exhibits 4.1 moles of fucose/mole Epo and 0.9 moles of N-acetylgalactosamine/mole Epo, while for r-Epo of Batch 2, the figures are 2.9 and 1.4, respectively.

39. In fact, there appears from these documents to be no certainty of getting a particular r-Epo glycosylation pattern. The glycosylation pattern for u-Epo would also appear to depend on the time of day, and physiological status of the patient from whom it is obtained. r-Epo thus appears to share with u-Epo the characteristic that the carbohydrate composition is to a considerable degree a matter of chance. Certainly the specification itself gives no incentive to obtain something different from u-Epo. As the aim is to produce biologically active Epo, a property u-Epo is known to possess, there seems to be no basis for assuming that each and every recombinant DNA process must produce something different. The statement by the Respondents' experts that r-Epo is inevitably different from u-Epo can only be taken as meaning that there are so many possible variations, and so little control of what comes out of any process of making the r-Epo that it is unlikely that any one r-Epo will have an absolutely identical

carbohydrate composition to any known u-Epo. This is not the same as it being impossible. For this Claim 19 to a polypeptide not limited to one which could be produced in a recombinant process using the DNA defined in Claim 1, the Board is not prepared at one and the same time to assume in favour of the patentee that everything within this very broad claim is disclosed in a manner sufficiently clear to be carried out except for something identical to the u-Epo of the prior art.

40. The Respondents' own submissions to the Food and Drug Administration (FDA) in the USA state that as far as biological and immunological activities go r-Epo and u-Epo are indistinguishable. The admitted error in the patent shows that at the priority date distinctions between r-Epo and u-Epo on the basis of glycosylation pattern were not necessarily reliable. The Respondents sought to rely on decision T 130/90 (*loc. cit.*), but in that case it was held that there was a reliable distinction introduced by a product-by-process feature. The situation is different here, and case T 130/90 is not authority for the proposition that every possible doubt as to whether a product-by-process feature necessarily implies a distinction must be resolved in favour of the patentee.

41. Claim 19 thus lacks novelty over the u-Epo of the prior art, and is not allowable. Therefore auxiliary request 2 containing this claim is not allowable.

Auxiliary request 3

42. Auxiliary request 3 contains as Claim 17 a claim with identical wording to unallowable (see points 32 to 41

supra) Claim 19 of auxiliary request 2. Therefore auxiliary request 3 is not allowable.

Auxiliary request 4

43. Auxiliary request 4 contains as Claim 3 a claim with identical wording to unallowable (see points 12 to 29 *supra*) Claim 3 of the main request. Therefore auxiliary request 4 is not allowable.

Auxiliary request 5: Clarity of Claim 19

44. Claim 19 of auxiliary request 5 is different from the Claim 19 of auxiliary request 2, already discussed above, only by the addition of the words "and not being identical to erythropoietin isolated from urinary sources." This claim is not based on any claim as granted so compliance with the requirements of Article 84 EPC must be checked.

45. The claim does not comprise any indication of the technical feature or the degree of difference on which non identity of r-Epo with u-Epo should be based, but rather leaves this to the reader's imagination. This puts the claim clearly in the category of claims which are not clear. The whole burden on distinguishing over the prior art u-Epo is put on the reader. In any case, if the reader were to start research to get reliable technical data to examine whether this condition is fulfilled, he would of necessity face all the difficulties discussed above in relation to Claim 19 of auxiliary request 2 (see points 32 to 41 *supra*).

46. Claim 19 of auxiliary request 5 is thus not allowable as not being in accordance with Article 84 EPC, and auxiliary request 5 must therefore be refused.

Auxiliary request 6

47. Auxiliary request 6 contains as Claim 17 a claim with identical wording to unallowable (see points 44 to 46 *supra*) Claim 19 of auxiliary request 5. Therefore auxiliary request 6 is not allowable.

Auxiliary request 7

48. Auxiliary request 7 contains as Claim 3 a claim with identical wording to unallowable (see points 12 to 29 *supra*) Claim 3 of the main request. Therefore auxiliary request 7 is not allowable.

Auxiliary request 8: Allowability of Claim 19 as amended

49. Claim 19 of auxiliary request 8 is based on a combination of Claims 20, 21 and 22 as granted, incorporating the limitations of dependent granted Claims 21 and 22 into granted independent Claim 20. This Claim 19 differs from Claim 20 as granted by the insertion of the word "recombinant" before "polypeptide" in line 1, by the deletion of the words "procaryotic or" in the reference to "characterized by being the product of procaryotic or eucaryotic expression of an exogenous DNA sequence" (this was the restriction made by granted dependent Claim 21), and the addition at the end of the claim of the feature "and having an average carbohydrate composition which differs from that of human erythropoietin isolated from

urinary sources" (this was the feature of granted dependent Claim 22).

50. The restriction derived from granted Claim 21 does not extend the scope of the claim. The insertion of "recombinant" is an anticipatory reference to the feature "characterized by being the product of eucaryotic expression of an exogenous DNA sequence" at the end of the claim, and does not extend the scope of this Claim 19 or make it any less clear. The further feature derived from granted Claim 22 does not extend the scope of protection. The combination of granted Claims 20, 21 and 22 into this Claim 19 of auxiliary request 8 thus does not contravene Article 123 EPC, and introduces no lack of clarity not already present in the claims as granted.

51. Taken by themselves the words "and having an average carbohydrate composition which differs from that of human erythropoietin isolated from urinary sources" seem to mean no more than "and not having a carbohydrate composition identical to that of human erythropoietin isolated from urinary sources" as there is no indication of what parameter(s) is (are) to be measured, how it (they) is (are) to be measured and how an average is to be calculated. That a reference to "average carbohydrate composition" is virtually meaningless, can also be deduced from the fact that it is a feature that the Respondents held not to deserve a place in the recapitulative Table of the distinguishing features between u-Epo and r-Epo found on page 20 of Cummings (P262).

52. In the description the only reference to "average carbohydrate composition" is at page 29 lines 29 to 30. The sentence in which it appears discloses nothing as to the meaning of "average carbohydrate composition", but its appearance just after the paragraph at lines 16 to 26 of page 29 referring to experimentally determined carbohydrate constitution values, suggests that the two probably refer to the same thing. Yet it is just this paragraph at lines 16 to 26 of page 29, that the Respondents admit gives quite wrong values. There is thus nothing in the description which taught what to measure: on the contrary, if the information given concerning carbohydrate constitution were to be relied on when seeking differences in average carbohydrate composition the skilled person would be positively misled.

53. As explained in points 39 and 40 *supra*, the Board is unable to accept that something different from u-Epo necessarily results from the recombinant process, so the feature "and having an average carbohydrate composition which differs from that of human erythropoietin isolated from urinary sources" being a measurable limitation is quite critical for the recognition of novelty. However, given that u-Epo is known to be of variable composition, the skilled person set the target of making something within this Claim 19 cannot do so because he does not know what test to apply. The claim is thus unallowable as contravening Article 83 EPC, and thus auxiliary request 8 must be rejected.

Auxiliary request 9

54. Auxiliary request 9 contains as Claim 17 a claim with identical wording to unallowable (see points 49 to 53 *supra*) Claim 19 of auxiliary request 8. Therefore auxiliary request 9 is not allowable.

Auxiliary request 10

55. Auxiliary request 10 contains as Claim 3 a claim with identical wording to unallowable (see points 12 to 29 *supra*) Claim 3 of the main request. Therefore auxiliary request 10 is not allowable.

Auxiliary request 11

Articles 123 and 84 EPC

Allowability of amendments

56. Of the thirty-one claims of auxiliary request 11 (see Annex I), only three, Claims 3, 19 and 26 differ from the claims as granted in matters other than the claim numbering and the claims on which the dependent claims among them are stated to depend. None of the oppositions was based on the ground of Article 100(c) EPC, that the subject-matter of the European patent extends beyond the content of the application as filed, i.e. contravenes Article 123(2) EPC. Accordingly for the purposes of Articles 123 and 84 EPC the Board need only consider these three Claims 3, 19 and 26.

Claim 3

57. Claim 3 of auxiliary request 11 results from rewriting as an independent claim, Claim 4 as granted which depended on independent Claim 3 as granted. No objection was raised against this being allowable under both Articles 123 and 84 EPC, and the Board sees none.

Claim 19

58. Claim 19 of auxiliary request 11 is based on Claim 20 as granted amended by the insertion of the word "recombinant" before "polypeptide" in line 1, by the deletion of the words "procaryotic or" in the reference to "characterized by being the product of procaryotic or eucaryotic expression of an exogenous DNA sequence" (this was the restriction made by granted dependent Claim 21), and the addition at the end of the claim of the feature "and which has higher molecular weight by SDS-PAGE from erythropoietin isolated from urinary sources." These amendments were objected to by some of the Appellants on the basis of both Article 123(2) EPC and Article 84 EPC. No objection was raised by the Appellants under Article 123(3) EPC that the claim had been amended in such a way as to extend the protection conferred, and the Board sees no such objection.

59. The objected feature "and which has higher molecular weight by SDS-PAGE from erythropoietin isolated from urinary sources" is a restriction compared to the scope of granted Claim 20, and the basis for this restriction is provided by the passage at page 29, lines 6 to 10 of the text of the patent as granted. The same passage appears in the text as filed. There is no objection to this under Article 123(2) EPC.

60. One Appellant objected that use of a term such as "higher" made this feature unclear and thus contrary to Article 84 EPC. However what is to be measured is clear. Values of the molecular weight of u-Epo measured by SDS-PAGE were part of the prior art. Frequently where something has to be measured there will be a grey area where measurement error may make it difficult to determine whether a particular product falls within a claim or not. This does not justify an objection under Article 84 EPC.

61. The insertion of "recombinant" is an anticipatory reference to the feature "characterized by being the product of eucaryotic expression of an exogenous DNA sequence" and does not make it any less clear. One Appellant submitted that it would be inconsistent for the Board to treat the product-by-process feature "recombinant" as introducing no limitation which would be suitable to establish novelty, and yet not objecting to this amendment under Article 84 EPC. The answer to this is that the Board is not entitled to prescribe the form of the claims put forward. Where an addition appears to the Board not suited to establish novelty but does not make the claim less clear, the Board is not prepared to delay proceedings by lengthy discussion of the matter, nor to revoke the patent on the basis of Article 84 EPC that claims have to be concise.

Claim 26

62. This claim corresponds to Claim 27 as granted with the words "procaryotic or" in the phrase "a polypeptide product of the expression in a procaryotic or eucaryotic host cell of a DNA sequence..." deleted. The

deletion of this alternative restricts the scope of the claim, is based on the original disclosure and the resulting claim is clear. Thus this amended Claim 26 is acceptable under the provisions of Articles 123 and 84 EPC.

Sufficiency of disclosure - Article 83 EPC

Claim 1

63. The issue of whether the patent disclosed the invention of Claim 1 in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, was the issue to which most written evidence and most time at the oral proceedings were devoted. The first question that needs to be decided is whether any practicable method of making something falling within Claim 1 has been disclosed at all.

64. The Respondents' witnesses (Dr Browne, Prof. Wall, Prof. Murray) accepted that the following steps would be necessary to make a DNA sequence according to Claim 1 coding for human Epo:

(a) obtaining an available gene bank, e.g., the Lawn gene bank (P79) or producing this in accordance with the published literature, such bank having a high probability of containing a clone including the gene sequence coding for human Epo.

(b) Making a DNA oligomer to act as a probe to isolate clones with the Epo gene from the gene bank.

(c) Isolating, sequencing and characterizing the clone.

(d) Obtaining available vectors, and constructing a suitable expression vector.

(e) Obtaining host cells in which the DNA could be expressed.

(f) Transfection of the host cells, amplification of the cells, and cultivation to produce Epo.

(g) Producing standard antibodies for an assay for Epo.

(h) Purification of the Epo so produced, and testing that it has the desired properties.

65. The skilled person must be in a position to carry out without undue burden not only all steps relating to the isolating and cloning of the DNA, but also steps (d) to (h) which relate to expressing the DNA, in order to produce Epo and to be able to check that the expression product is indeed Epo coded by the DNA sequence claimed in Claim 1. In the following the Board briefly compares the above steps with the examples given in the patent.

Examples 1 to 3

66. Examples 1 to 3 show the first steps of the whole process of how the Respondents arrived at the invention. These are not steps that the person seeking to put into effect the invention has to carry out, given that he could rely on precise information on

suitable probes deducible from Tables V and VI and that there is sufficient guidance by starting with Example 4.

Example 4

67. Example 4 is directed to procedures involved in the identification of positive human genomic clones and thus provides information concerning the source of the genomic library, plaque hybridization procedures and verification of positives clones. This is information that would assist with step (a) *supra.*

Example 5

68. Example 5 is directed to DNA sequencing of a positive genomic clone and the generation of human polypeptide amino acid sequence information including a comparison thereof to the monkey Epo sequence information. This example, and in particular Table VI to which it refers, will enable step (b) of making an oligomer probe to be carried out with a long probe which can be expected to hybridise uniquely with and identify the colony of the gene library containing the gene for Epo.

Example 6

69. Example 6 is directed to a procedure for construction of vectors incorporating Epo-encoding DNAs derived from a positive monkey cDNA clone, and the use of the vector for transfection of COS-1 cells and cultured growth of the transfected cells. It is not of direct relevance to carrying out steps (a) to (h).

Examples 7A, 7B and 10

70. As has been pointed out by the experts called by Appellant 05, e.g. Dr Sytkowski, expression of DNA in COS and CHO cells, and the vectors to be used had already been discussed in the prior publication of Rigby (P360-8), and what the patent suggested in Examples 7A, 7B and 10 was essentially using this published method for expressing the DNA sequence coding for Epo. While the publication Rigby is not explicitly referred to, the Board accepts that in this art the skilled person would be aware of this source of information relating to the use of COS and CHO cells and would rely on this for any additional information needed in carrying out steps (f) and (g) *supra*.

71. Steps (e) and (h) in general involved the application of known techniques, which with the information given in Table VI on the protein structure of Epo could be applied by the skilled person without the need for more detailed instructions.

Examples 8, 9 and 11

72. These examples provide no additional information of use for carrying out steps (a) to (h) *supra*.

73. The Board considers that *prima facie* the information given is sufficient for a DNA sequence coding for human Epo in accordance with Claim 1 to be obtained on the basis of the instructions in the patent and the common general knowledge in the art at all. It was not argued by the Appellants that a DNA sequence coding for monkey Epo could not be made.

Particular aspects of sufficiency of disclosure

74. On behalf of Appellant 04, however, Prof. Straus and Dr Moufang (P316) have submitted that Article 83 EPC requires that clones containing the Epo gene, possibly already combined with suitable expression vectors, must be made available by the Patentee to the public by deposit under Rule 28 EPC if this would allow the invention to be reproduced very much more quickly than by following only the instructions of the specification. Such a deposit was all the more necessary in a case, such as this, where omissions, errors and traps contained in the examples would otherwise cause delay in reproducing the invention. Lack of a deposit meant that the invention could only be reproduced with an undue burden which has to be equated to no enabling of the invention at all. This proposition finds no support in the wording of Rule 28 EPC:

"(1) If an invention concerns a microbiological process or the product thereof and involves the use of a micro-organism which is not available to the public and which cannot be described in such a manner as to enable the invention to be carried out by a person skilled in the art, the invention shall only be regarded as being disclosed as prescribed in Article 83 if..."

Here the invention can be carried out without a deposit.

75. Nor is there any support for this proposition by any case law, or by the reports of the Munich diplomatic

conference on the introduction of a European patent grant procedure or other preparatory documents for this. The preparatory documents (see for example M/PR/I paragraphs 2102 to 2201, in particular paragraphs 2107 and 2124) make clear that the deposit related to inventions that could not be carried out unless a microorganism was deposited, because in the then state of the art an adequate description was not possible. It was realised as a disadvantage for the patentee that this would make it easier for others (potential infringers) to reproduce the invention than was the case in most fields, but the choice lay between this and others not being able to repeat the invention **at all**. There is no suggestion that deposit should be for the purpose of making something already possible easier.

76. This need for a deposit cannot be introduced by reference to the concept of undue burden. This concept relates more to cases where the route that the reader is to follow is so poorly marked that success is not certain (see Decision T 418/89, OJ EPO 93, 20). If the route is certain but long and laborious, the patentee is under no obligation to assist the disclosure by making actual physical samples, i.e. the "factory" available. To come to the opposite conclusion would be effectively to introduce a requirement to make the best mode immediately accessible to the public, and such a requirement is not part of the European Patent system.

77. It was indeed conceded by the Appellants that relying only on common general knowledge and the information in the patent, a skilled person would arrive at a product falling within the claim, but only after having spent

so much time and effort in doing so, that it amounted to undue burden so that Article 83 EPC was not complied with.

78. In support of undue burden the Appellants (see in particular, the Declaration of Prof. Straus and Dr Moufang (P316, pages 6 to 8, Sections 2.4 to 2.4.3), and also the Declaration of Prof. Hofschneider and Prof. Straus (P337a, page 39, Section IV)) essentially brought forward the argument that, owing to the patentee's failure to deposit clones comprising the genomic DNA sequence coding for human Epo that the patentee had isolated, the skilled person wishing to reproduce the invention had to follow exactly the one way shown in the description and in particular Examples 7B and 10. However, because these examples contained errors and omissions the skilled person either would have failed altogether, or would have had to spend an undue amount of time and effort in doing so, namely in the order of five years.

79. During the proceedings, both Appellant 05 and the Respondents provided time estimates of the time it would take, reproduced in overhead "Oral 20" (pages 932 to 933 of the Appeal File). Overhead "Oral 20" is a time table provided by Appellant 05 and based on Prof. Flohé's Declaration (see P339), on which time table the Respondents also entered their own time estimates for comparative purposes.

80. But this is not the only information made available to the Board on the time taken to reproduce the invention, as this case has the unusual feature that although the patent specification contains very much more detail

than the prior art on how to make the claimed product, the validity of the patent is being challenged on the grounds of both obviousness and insufficiency. While Opponents certainly may have good reasons to rely on both grounds, evidence put forward in favour of one of these grounds of opposition may conflict with evidence in support of the other ground of opposition. Here this has particularly occurred with the evidence on the amount of time that various steps would take. The Board is aware of the fact that the time estimate of Appellant 04 was established on the assumption that the skilled person would have followed exactly the description containing errors, whereas that of Appellant 05 was based on prior art and common general knowledge and thus is not directly comparable. There are, however, time estimates provided by Appellant 04 which are not related to examples containing errors or omissions and thus can be compared with experimental time provided by Appellant 05.

81. In its attempt to demonstrate obviousness, Appellant 05 has provided a report of experimental work carried out by Dr Grundmann with two assistants. Apart from the method used to identify a clone containing a desired genomic sequence coding for Epo, the steps taken were the same as those necessary to put into practice the invention in accordance with the patent specification, and the techniques used were ones that might have been used to carry out the invention, as Dr Grundmann had deliberately chosen techniques available before the priority date of the patent. Therefore, the time needed by Dr Grundmann provides an experimentally verified basis for estimating how long it would take to carry out the invention. This time period coincides with the

estimates put forward by the Respondents' experts, and was very much shorter than those estimated by the experts for Appellant 04. This conclusion was arrived at on the following basis, which also takes into account the Board's disagreement to the Appellant's 04 opinion that the skilled person had, owing to the lack of deposit of Epo DNA clones by the Patentee, to follow exactly the Examples as a recipe and that, as a consequence, the error and omissions affecting the description would have resulted in a heavier burden than if no examples were present at all.

82. The First Experimental Test reported by Dr Grundmann in P231 cannot have been started before 3 December 1991 (since Dr Grundmann had of necessity first to see the revised version of Dr Lathe's DNA probe: see page 1 of P231) and was completed, at the latest on 11 June 1992 the date of declaration P231.

83. The time between these two dates amounts to about 25 weeks, necessary for an assistant under supervision of Dr Grundmann, to:

- synthesise a 81-mer DNA probe

- screen a genomic-library (available from Stratagene) of 2.6×10^6 phages

- re-screen and dot-blot-screen the above library to isolate 5 positive signals

- identify and sequence 3 of the above positives.

Although Dr Grundmann is dealing in declaration P231 with a "long guessmer probe approach" (rather than the accurate long probe that can be used by using the information in Table VI of the patent), it is reasonable to assume that following the instructions of the specification and using absolutely correct probes would, if anything, shorten the time needed. According to the above mentioned overhead "Oral 20", the above steps would have required

2 weeks + 12 weeks + 30 weeks = 44 weeks (Appellant's 05 figure for one person) or

1 week + 4 weeks + 4 weeks = 9 weeks (Respondents' figure), in the case of a three person team.

84. The figure that can be deduced from Dr Grundmann's declaration P231 (25 weeks x 1 person) is consistent with the Respondents' (9 weeks x 3 persons = 27 weeks x one person), while it is not consistent with that of the Appellants.

85. In line with the above, Dr Grundmann's Second Experimental Test (P253) cannot start before he received the third genomic-DNA bank on 4 June 1992 (see page 3) and must have been completed, at the latest on 15 September 1992 (date of declaration P253). The time period between these two dates (about 14 weeks) was spent by an assistant, supervised by Dr Grundmann, in performing essentially the same work as in P231. Again the time figures are consistent with those given by the Respondents' experts (see "Oral 20"), while they do not agree with those given by the Appellants' experts.

86. The same conclusions are forced upon the Board even more strongly by Dr Grundmann's Third Experimental Test (P252), which cannot have been started before 26 August 1992 (see page 1) and was completed, at the latest, on 30 September 1992 (date of statement P252): 4 weeks were required to accomplish the same work as in P253.

87. Further, the Experimental Report from Biopharm GmbH (P209) shows that it is possible to construct 3 oligonucleotides and screen a Lawn gene bank in 1 month with a 3 person team ("3 Mannmonate": see page 8) or to prepare a genomic library in one month with 2 men ("2 Mannmonate": see p. 8). These figures are consistent with the Respondents' figures, while they are in disagreement with those provided by the Appellants (12 weeks for constructing a genomic-library). This also shows that the commercial availability of a Lawn gene bank was not critical.

88. Report P209 also gives forecasts on how long it would take for making the vectors, cells, etc. The Board, however, believes that preference should be given to true experimental data, rather than to mere theoretical forecasts.

89. The Appellants provided evidence (P339) that it would have required 66 weeks for a team comprising a scientist and two technicians to carry out Example 4, relating to the identification of positive clones (see point 67 *supra*).

90. However, Prof. Orkin's statement (see P280, Section 16) that the genomic cloning was completed within a few

months, seems to be more realistic than 66 weeks. The time estimate of a few months is reasonably consistent with the Wojchowski paper (P281) and Dr Sytkowski's Declaration (P289, Section 7 to 14), the latter being an Appellants' expert, according to whom the **whole** process leading to r-Epo expression does not require more that 2 years at most. Therefore, it seems unlikely that the cloning process alone required 66 weeks, as the Appellants maintained.

91. Further there is also the evidence available concerning work done by Genentech, one of the leading companies in this field, who had instituted a research programme to find a recombinant route to Epo, which was finally abandoned as unsuccessful after the expenditure of several million dollars. Two of the people involved in that work gave evidence, Dr Sytkowski on behalf of Appellant 05 and Prof. Orkin on behalf of the Respondents. These two together with Dr Wojchowski also published a paper (P281) concerning certain further work they did after the abandonment of the project, when the DNA sequence of Epo was published. Relying only on a sequence equivalent to that published in Table VI they were able to carry out essentially all of steps (a) to (h) in a matter of a few months. This is support for the conclusion that the calculations of the time needed provided by Appellant 05 were too pessimistic.

92. Of the steps (a) to (h) necessary to carry out the invention of Claim 1, the main blockage which prevented those who were actually trying to make Epo by a recombinant DNA route from succeeding before the priority date of the patent was step (b), as they were

unable to a make a probe which could identify the gene coding for Epo. Potentially there was a further blockage that researchers might have met, if a very special cell system had been needed to express the DNA sequence in order to obtain Epo with a glycosylation pattern that produced in vivo activity. However on the evidence before the Board, COS cells and CHO cells produce such an Epo and these cells are indicated in the patent. Thus the most important bit of essential new information that the person skilled in the art needed was the sequence information provided by Table VI. The other steps involved applying known methods to this particular case. The evidence of Prof. Flohé (P339) for Appellant 04, shows that whether carried out in 1983 or 1994 the steps involved consumed substantially the same amount of time: this still leaves the patent in suit with the merit of having removed the blockage on step (b). That the patentee had not reduced the time it took to carry out other necessary steps by methods already known for other DNA sequences cannot, in the Board's view, mean that Article 83 EPC has not been complied with. The Board cannot agree that there is a requirement in the EPC that a Patentee who provides new information that for the first time allows certain methods to be applied to produce a new protein by way of recombinant DNA techniques, has in addition to improve on the time that it takes to carry out each of these known methods.

Example 5

93. Since, however, the core of Appellant's 05 argument on insufficiency was, that under the given circumstances the skilled person would have followed the description

like a "recipe" and would have failed because of the errors in certain examples the Board now turns to this particular situation. Example 5 is directed to DNA sequencing of a positive genomic clone and the generation of human polypeptide amino acid sequence information including a comparison thereof to the monkey Epo sequence information. With a view to Example 5, the Appellants (see eg, Prof. Schaffner Declaration (P204)) submitted that the errors and omissions affecting Table VI of the patent would render impossible the identification by restriction enzyme mapping of the gene looked for.

94. The Respondents, however, have reasonably demonstrated that the restriction map of the sought gene would have varied only slightly over that disclosed in the patent. In fact, Figure 2a of the Integrated Genetics patent EP 267678 relating to the restriction map of the Epo gene shows that 2 out of 18 restriction sites of the Epo gene diverge from those of the patent in suit. The Appellants' expert, Prof. Schaffner (P204) made use in his test of 8 restriction enzymes, 4 of which were known in 1983. The remaining 4 restriction enzymes (NspBII, PpuMI, SnoI and GsuI) can be regarded as "exotic" (see Prof. Murray's Declaration P156, page 8). Therefore, the Appellants' statement that the skilled worker, owing to the error in Table VI of the patent, would have difficulty in identifying the gene looked for by restriction enzyme mapping, is not convincing.

95. As to the Appellants' submission that the errors and omissions in the non coding regions of the Epo genomic sequence of Table VI would affect mRNA processing by the cell, the Board finds convincing Prof. Old's view

(see P203, Section IV.3), also shared by Prof. Weissmann (P287, Section 4.2) that the above deficiencies would be important only in the instance of a chemical synthesis of the gene but not if one isolates the DNA from a human genomic library using oligonucleotide probes corresponding to exon sequences depicted in Table VI. In the latter case, the genomic DNA fragment that is picked up comprises the correct sequence. Any sequencing mistake here would not influence this result, and it is not likely that the gene would have been discarded on the basis of slight divergencies, as confirmed by Prof. Weissmann (P287) and Prof. Murray (P156).

96. The Board is of the opinion that for these reasons the mistake in the sequence would not have been fatal and arriving at the information provided by Tables V and VI removed the blockage in the way of someone seeking to express Epo.

97. The above view of the Board finds support in Prof. Orkin's Statement (P280, Section 16) and Dr Sytkowski's Declaration (P289, Section 7 to 14), which have been made on behalf of the Respondents and Appellants, respectively, and do not diverge when focusing on an experimental work made in common and published as the Wojchowski paper (P281).

98. It transpires from P281 (see page 225, under the heading "Material and Methods" and page 228, right hand column, lines 2 to 3) that Prof. Orkin and Dr Sytkowski encountered no particular hindrances in carrying out the following operations (how long these operations take has already be dealt with in point 90 *supra*): they

first use an oligonucleotide probe with a sequence corresponding to the first 30 nucleotides of exon IV of Table VI. They pick up a positive clone and identify it in the light of the Jacobs' (P63) Epo sequence, which essentially corresponds to that of Table VI of the patent in suit. After having subcloned an Epo gene-containing fragment in plasmid pUC 19, a 3.6 kb 5'-BstEII-BamHI-3' fragment is inserted into the SV40-derived expression vector pSV2, available since 1981 (see reference [27] of P281). COS cells are transfected with this construct termed pSV2-epo^g and the transfected cells secrete 176±10 U/ml Epo. Once the Epo genomic sequence is available, anybody can choose at will the best suited probe(s). This situation cannot be compared with the use of a guessmer in this instance the Epo DNA sequence is not known.

Example 7A

99. Example 7A is directed to procedures for construction of vectors incorporating Epo-encoding DNAs derived from a positive human genomic clone, the use of the vector for transfection of COS-1 cells and cultured growth of the transfected cells. The Appellants essentially argued that the above mentioned vectors could not be reproduced. The Board, however, is of the opinion that the Examples give sufficient information for one skilled in the art in late 1983, when recombinant DNA technique was in an advanced development and many vectors were already known, to construct equivalent vectors useful for expressing Epo in mammalian cells. It is not necessary to use the same vector or to obtain the exact pBR322 fragment, as long as it comprises the bacterial origin of replication and the ampicillin

resistance gene: all this information as well as the exact restriction map of pBR322 can be taken from Prof. Maniatis' book (P171) published 1982, wherefrom it can also be seen that pBR322 exhibits a unique BamHI site for inserting a fragment. In any case, Wojchowski (P281) has been able to construct an equivalent plasmid. As regards plasmid pEpo303 constructed by Dr Schumacher (P207), the Board accepts that much work has to be done to prepare this vector but, eventually it was possible.

100. In respect to the vectors, and the COS and CHO cells, these were commercially available. Moreover, Rigby (P360-8) described as of 1982 a great many viral vectors, including the SV40 vector used in the patent.

Example 7B

101. Example 7B represents an alternative expression system to the one of Example 7A. It differs therefrom by the use of the SV40 late promoter and of a synthetic linker (containing SalI and BstEII sticky ends and an internal BamHI recognition site) for inserting the Epo gene into the intermediate plasmid pBRgHE.

102. In connection with the Appellants' attack on Example 7B, the Board finds convincing the Appellants' reasoning that the skilled person willing to reproduce Example 7B would of necessity synthesise a wrong BstEII-BamHI-SalI linker, once the latter is constructed in the light of Table VI of the patent, affected by an error at the 44th base 5'-wards from the ATG start codon. The consequences of the C...C mismatch that would result from the above wrong linker, are not

clear to the Board, in view of the contradicting experimental results provided by the parties. According to Prof. Schaffner's Report (P204, page 8), no ligation product can be obtained, while Dr Browne's (P158) and Dr Morris' (P159) tests yield the opposite result. Further, the Board has difficulties to judge the results given in Dr Schumacher's report (P210) relating to vector pEpo148 which was successfully used for producing Epo.

103. However, the Board notes that the linker of Drs. Browne and Morris is longer by 3 additional bp over that disclosed in the patent: this expedient serves, according to Drs. Browne and Morris, for preventing formation of linkers with two BstEII or two SalI ends by autohybridization.

104. The Board finds that the Appellants' line of argument that the above expedient is neither disclosed by Example 7B nor by the prior art, is convincing. It must be concluded that Example 7B is not reproducible and the above Board's view seems to be supported by Example 8, wherein the supernatants from Examples 6 and 7A are tested in the RIA for Epo, however, no product from Example 7B is subjected to the above assay.

Example 10

105. Example 10 is directed to the development of mammalian host expression systems for monkey Epo cDNA and human genomic DNA in CHO cells and to the immunological and biological activities of products of these expression systems as well as characterization of such products.

106. Insofar as the same flawed plasmid as in Example 7B is used, the Board has to conclude that Example 10 is also not reproducible. Otherwise, as long as Example 10 deals with viable plasmids, the Board believes that the Appellants' statement that it is impossible to obtain the same glycosylation pattern, is immaterial to the Article 83 EPC question. The Board indeed observes that even if the glycosylation pattern depends on the cell system used for expression, r-Epo secreted from a different CHO DHFR$^-$ cell is expected to exhibit a proper glycosylation pattern (see Prof. Chasin's Declaration P364, p.6) and, hence, to be active. It will thus fall within the scope of the patent claims. The principle according to which fluctuations in yields, quality, etc, of a claimed product are irrelevant to the Article 83 EPC issue unless the invention requires certain characteristics in this respect, has already been affirmed in Decision T 281/86 (*loc. cit.*).

107. As to the Appellants' submission that it is not possible to repeat the Example, it is contradicted by the Wojchowski paper (P281). While Figure 1 illustrates the difficulties encountered for preparing a human Epo cDNA, it seems to be possible without any unusual difficulties to manufacture plasmid pSV2-epo^g for use in transfecting a COS cell (see page 225, right column, bottom).

108. As far as the wrong sugar analysis given in Example 10 is concerned, the Board accepts that the skilled person would take into consideration (see Prof. Kamerling's Report (P365, page 13 of the translation)) that the analysis rather than the product is wrong, on the basis

of the *in vivo* activity and the SDS-PAGE gel, the latter being not in contradiction with the carbohydrate analysis, and thus he would not discard the recombinant product.

Examples 11 and 12

109. Example 11 is directed to the preparation of manufactured genes encoding human Epo and Epo analogues, which genes include a number of preference codons for expression in *E. coli* and yeasts host cells, and to expression systems based thereon. Example 12 relates to the immunological and biological activity profiles of expression products of the systems of Example 11.

110. Examples 11 and 12 show the use of what is called the synthetic approach for preparing Epo genes comprising bacterial or yeast preference codons. The above Examples thus support the feasibility of one embodiment of the claims, namely the altered DNAs comprising *E.coli* and *S. cerevisia* preference codons.

111. It is true that, on the Respondents' own admission, the glycosylation pattern of the r-Epo of Examples 11 and 12 is not properly reported and *in vivo* activity of the given pattern is not ensured. However, in the Board's view, this represents no bar for the altered DNAs of Examples 11 and 12 to fulfil the requirements of Article 83 EPC, for the reasons given in point 108 *supra* and since Claim 1 anyhow is not restricted to DNAs encoding *in vivo* active Epo (see point 121 *infra*).

112. In conclusion, the Board is of the opinion that the skilled person is able to reproduce the invention in the light of the Examples, even in the instance the patent disclosure has to be viewed as a recipe. The Board accepts that the disclosure of the patent still requires the public to invest a lot of time and effort, which, however, does not in the circumstances given amount to an undue burden. As shown above, the errors and omissions indeed prejudice the reproducibility of Example 7B *in toto* and of Example 10 in part. However, Example 7B and Example 10 (the latter only insofar as it involves the same flawed plasmid as Example 7B) are alternative ways to Example 7A and Example 10 (involving the correct plasmid). The Appellants did not succeed in convincing the Board that the deficient examples resulted in an uncertainty of reproducibility which would amount to undue burden and that the remaining Examples, leading to the expression of *in vivo* active r-Epo cannot heal this particular situation. Therefore, the Appellants' line of arguments for questioning the patent under Article 83 EPC cannot be sustained by the Board.

113. The Appellants argued that the scope of Claim 1 still covered human cDNA, and that if the Board came to the conclusion that Claim 3 as granted was invalid because the patent did not disclose a manner sufficiently clear and complete for it to be made, then Claim 1 comprising not sufficiently disclosed subject-matter necessarily also contravened Article 83 EPC.

114. This line of argument ignores two points. Firstly on the definition that the Board gives to the term cDNA, this requires a cDNA to be something having the

property that it can be identified as being the same sequence as obtained by reverse transcription from mRNA. This in turn requires a route to a mRNA to be identified. The Board decided that this route was not disclosed in an enabling manner (see points 11 to 29 *supra*). This reasoning includes that there was no sufficient disclosure of what the cDNA coding for human Epo was. The evidence put forward does not allow the Board to come to any safe conclusion that a particular DNA sequence described is the human cDNA and that it falls within Claim 1. The Board cannot assume from the mere existence of dependent Claim 3 as granted that cDNA necessarily falls within Claim 1.

115. Secondly, the advantage in the cDNA appears not so much to lie in the sequence itself, but in having a route via mRNA by which this sequence can be obtained.

116. The claims of auxiliary request 11 must thus be considered as fulfilling the requirements of Article 83, EPC.

Novelty

117. In decision T 301/87 (*loc. cit.*, see reasons section 5) there has already been discussed the question of whether in 1980, the unknown presence of a particular nucleotide sequence in a Lawn gene bank could be regarded as state of the art for the purpose of Article 54(1) EPC. On the facts then, it was found that this was not the case in the absence of a known probe, or any other means, enabling the sequence to be identified. Apart from the relevant point of time here being some three years later, the relevant facts are

virtually identical in the two cases, and general knowledge in the art concerning gene banks did not significantly change in this period. Accordingly as in this case too, no probe was known for identifying the relevant gene, the Board finds that the nucleotide sequence of the Epo gene was not part of the state of the art merely because the nucleotide sequence would have been present in the Lawn gene bank or possibly others.

118. As to the Sugimoto (P125) disclosure, which is the only document said to anticipate the claims to transformed host cells and to the process, the Board agrees with the Respondents that a cell fusion process, such as that disclosed by P125, cannot be equated to the transfer of purified exogenous DNA. The claims to DNAs, host cells and the process are thus novel.

Novelty of Claim 19.

119. The more precise definition according to which the polypeptide should exhibit a higher molecular weight by SDS-PAGE from erythropoietin isolated from urinary sources is a restriction in the claim. It has now to be examined whether it is a reliable parameter for the assessment of novelty. The r-Epo preparations claimed, must show by SDS-PAGE a higher m.w over the highest m.w by SDS-PAGE of the u-Epos made available to the public. In the Board's opinion, the fact that the Respondents have chosen this "yardstick" does not lead to a situation of legal uncertainty for third parties, because it is reliably possible to check on a SDS-PAGE gel whether a given r-Epo exhibits a higher m.w than a given u-Epo made available to the public. The Board

further observes that the support for Claim 19 in the description (Example 10, page 29, lines 6 to 10) is not in contradiction with the carbohydrate analysis referred to on lines 23 to 25, which is wrong: the SDS-PAGE gel results are fully consistent with the test with neuraminidase mentioned on lines 11 to 12 on the same page.

120. As regards Epo secreted by fused cells (P125) and by the RCC-3-JCK tumour cells (P111), the Appellants have not been able to provide evidence about either the true nature of the product, or the enabling character of the teaching of P125 and P111. Regardless of whether the cells are publicly available or not, the Board cannot take it as proved that these cells secrete an Epo supernatant comparable to that of the present invention. Taking into account the Appellants' strongly relied on argument made in connection with the inventive step question, that, in contrast to the general unavailability of significant amounts of purified Epo for structural studies to the scientific community, Dr Goldwasser provided the Respondents with u-Epo in amounts sufficient to carry out reasonable sequencing experiments, and hence, the Respondents succeeded in cloning the Epo gene while other scientific investigators met with a failure (see eg, P295, paragraphs 10 and 11 and P360, Section 3), the Board must conclude that no source of Epo other than u-Epo was available to the public in 1983. In view of the above, the information made available in documents P125 and P111 cannot be regarded as destroying the novelty of the subject-matter of Claim 19 of this auxiliary request. Therefore, Claim 19 and dependent claims fulfil the requirement of Article 54, EPC.

Inventive step of Claim 1

121. The closest prior art is represented by Miyake (P89) and Sasaki (P113). Document P89 discloses a seven-step purification process of u-Epo from 2,550 l of urine of patients with aplastic anaemia yielding milligram quantities of u-Epo in a state of apparent homogeneity and with a specific activity of 70,400 U/mg. Document P113 discloses the purification with immunoadsorbent column of u-Epo from 700 l of anaemic patients to yield 5.6 mg of u-Epo with a specific activity of 81,600 U/mg *in vivo*. The processes described in documents P89 and P113 have to be considered to be unsuitable for the manufacture of Epo in quantities for use in therapy. Therefore, in analogy to the situation dealt with in decision T 223/92 (*loc. cit.*) the technical objective problem can be stated, for the claims to the DNA sequences, as being making available the means or the tools to enable the manufacture of Epo in quantities sufficient to meet the demand for Epo for extended clinical studies and for therapeutical applications. Before the Board discusses the experiments provided by the Appellants to evidence that no inventive step is involved in the provision of the DNA sequences, it would remark that in any case the fact that the DNAs code for possibly non novel subject matter does not *ipso facto* mean that there is no inventive step in the provision of the DNAs and consequently, of any process, plasmid or transfected cell involving or comprising said DNAs. In Decision T 500/91 (*loc. cit.*) the Board did not reject the claims to the DNAs, plasmids and recombinant processes because interferon-α was a known protein. The claims to the DNAs and dependent claims here still comprise the term "procaryotic" implying the

preparation of aglyco-Epo, unlike the claims to the polypeptides *per se*. Although in its communication (see Section IV *supra*) the Board had preliminarily taken position that this type of Epo was not novel and thus not patentable as such, the provision of DNAs as means for the production of the valuable albeit not patentable aglyco-Epo, therefore, does not necessarily render the DNAs obvious.

Availability of mRNA and thus feasibility of the cDNA-route to the invention

122. The Appellants relied on the immunoprecipitation approach of Korman (P73) for questioning the inventive step. The Korman technique consists of using an antibody against Epo (P121) in order to precipitate the polysomes which possibly could provide a sufficiently enriched source of mRNA. The Board is of the opinion that this argument is not convincing, in view of submissions by Appellants and Respondents that there was no known feasible source of Epo mRNA, at the priority date of the patent see (Prof. Wall (P155, Section 19), Browne (P'183, paragraph bridging left hand and right hand column of page 693), Dr Hirt (P202, bottom of page 2) and Prof. Schaffner (P205, item 6)) on which this immunoprecipation could have been tried. In view of the above, it cannot be concluded that the antibody described in P121 was capable of immunoprecipitating Epo polysomes, and thus of mRNA to which ribosomes adheres. So this was not a route by which sufficient mRNA for the preparation of r-Epo via the cDNA-route could have been obtained.

The mixed short probe approach

123. With a view to the degenerate mixed short probe approach of Seki (P116) (see Section VI (ca), approach B *supra*), the Board is of the opinion that said approach would not reasonably have been expected to enable isolating the Epo gene from a human genomic library in late 1983, on the following grounds: Anderson (P3, paragraph bridging the two columns of page 6838) seems to demonstrate shortly before the priority date of the patent a scientific community's prejudice about applying the mixed short probe approach to the screening of genomic rather than cDNA libraries: owing to the mixed probes' lack of specificity required for probing something as complex as a mammalian genome, this method was believed impractical for the isolation of mammalian genes. The fact that only one piece of prior art literature dealing with the mixed short probes approach applies to a genomic library, namely document P116, appears to confirm the Board's view that the vast majority of those skilled in the art refrained, before the priority date of the patent, from any use of the mixed short probes technique for screening a genomic library.

124. The Respondents emphasized that Seki's attempt to isolate a gene from a genomic library using degenerate mixed short probes, was a failure (Declaration of Prof. Silver (P157)), owing to the presence of an intron (P174). This knowledge of failure could not have permitted a reasonable expectation of success. The Appellants, however, maintain, supported by a declaration of Prof. Schmieger (see P229, Section 6) that the person skilled in the art had no knowledge of

Seki's failure before the priority date of the patent. The Board can agree to Appellants' expert, Prof. Winnacker's (P179, item 4) statement that nothing in the abstract of P116 suggested that the experiment was unsuccessful. However the Board has to complete the above statement by adding that nothing in the abstract of P116 suggested that the experiment was successful either. P116 was in fact a provisional publication (abstract). The Board finds it doubtful whether the disclosure of the abstract would have given the skilled reader an impression of success by Seki. The abstract reads: "...This suggests that our clone contains DNA sequences of ....the DRα subunit....DNA sequencing of this region of the clone is presently underway to confirm the presence of the structural gene for the DRα subunit. This will be the first example of isolation of a mammalian genomic clone using direct screening with synthetic oligonucleotide probes". The term "suggests" is not equivalent to "demonstrates" and the future tense "will be" does not mean "is". In other words, this statement leaves open whether the clone that has been picked up, will turn out actually to be the DRα gene. It seems rather reasonable to assume that the skilled person wishing to put into practice the Seki's teaching, would have first awaited confirmation of the author's success, before investing time and money in this approach.

125. For the screening of a genomic library for the DRα subunit, Seki (P116) used two sets of 48 16-mer and 16 14-mer oligonucleotide probes. In contrast to that, in the patent in suit, two pools of 128 20-mers and 128 17-mers are used. The Seki's set of probes cannot be seen as highly degenerate when compared with those used

in the patent in suit. The possibility of errors in the synthesis of multiple oligonucleotides and thus also the background noise on the screening matrix or filter, increases with the number of probes in the pool. Since nobody had previously screened a genomic library with two pools of probes of such a high degeneracy, it was not possible to forecast whether a high background of radioactivity would make it impossible to discern the positives.

126. Further to the above facts, which by themselves speak in favour of an inventive step of the Respondents' screening procedures, the Board has to observe that the inventor ascribes his success (see P82, page 7582, last paragraph; see also the patent specification, page 45, lines 46 to 57) to "the optimization of various steps in the hybridization....Proteinase K digestion greatly reduced the nonspecific background, which made probing with a mixture of 128 sequences possible".

127. Although Seki (P116) used probes of lower degeneracy, what he considered to be a positive clone turned out upon sequencing to have no relationship with the gene looked for (Prof. Silver's Declaration (P157, Section 8)). Seki's method was not one that was obvious to adopt for screening a genomic library because there was no indication that it would have been successful. There was even less incentive to try the even more complicated method used by the Patentee.

128. Turning to Epo amino acid sequence information, the Board cannot agree to the Appellants' arguments that obviousness of isolating the human Epo gene depended decisively on the availability of Epo amino acid

sequence information, in particular on whether there was reliable Epo amino acid sequence information before the priority date of the patent, or whether everybody was in a position in 1983 to sequence Epo or fragments thereof with a high degree of reliability. In fact, amino acid sequence information proved unreliable and not useful before the priority date of the patent. The Sue (P121) sequence comprised two errors. Yanagawa's (P150) sequence contained 16% of errors or omissions upon using the best sequencing technique available at that time. Biogen's unpublished attempt to re-sequence Epo also yielded an error at position 24 (P164 page 1760, right column). The Respondents maintain that while the Epo tryptic fragments were available to anybody, it could not be taken for granted that any tryptic fragment would have proven useful to the screening procedure, owing not only to errors in the sequencing procedure, but also to the presence of introns. The Board observes that the inventor was not successful with the 15 fragments Dr Goldwasser obtained by subjecting Epo to enzymatic cleavage and HPLC purification (see P164, page 1747, right column). The inventor was successful only with probes EpV, Epo-17 and EpQ designed in the light of amino acid sequence information that Dr Por Lai had been able to take from Dr Goldwasser's additional tryptic fragments (see P164, *loc.cit.* and Dr Por Lai's First and Second Declaration (P298, Section 5.c and P299, Section 2)). As regards Dr Por Lai's submissions, the Board notes that they have been introduced into the appeal proceedings for the purpose of showing obviousness and reliability of the sequencing techniques as of late 1983. However, Dr Lai states (P298, Section 5.b) that his contribution to the Patentee involved the development of novel

protein microsequencing techniques necessary for working with tiny quantities of Epo and fragments thereof (see also *ibidem*, Section 9: "..my **novel** microsequencing methods...") (emphasis added).

129. The above statement is fully consistent with his later publication P'160 (see page 3119 to 3120, under the headings "Supplemental material" and "References"), wherefrom it transpires that Dr Por Lai probably used a sequencing technique not available to the public before the priority date of the patent.

130. Therefore the Board would not define Dr Lai's work as average technician's routine sequencing work.

131. In conclusion, it seems very unlikely that the skilled person was in a position to obtain reliable sequence information by routine sequencing techniques available in late 1983.

132. The Appellants strongly relied on the argument that, in contrast to the general unavailability of significant amounts of purified Epo for structural studies to the scientific community, Dr Goldwasser provided the Respondents with u-Epo in amounts sufficient to carry out reasonable sequencing experiments, and hence, the respondents succeeded in cloning the Epo gene while other scientific investigators met with a failure (see eg, P295, paragraphs 10 and 11 and P360, Section 3).

133. The Board, though, notes that the Miyake (P89) and Sasaki (P113) publications belonged to the prior art. Epo was thus available or potentially available to anybody, albeit in tiny quantities. Dr Por Lai started

from only 565 µg Epo for correctly sequencing the protein, see P'160, page 3116, under the heading "Discussion", while Yanagawa could theoretically avail himself of about 5.6 mg Epo, (P113, Table II and P150, Table I). Had the Respondents enjoyed the advantage the Appellants maintain they had, this would not lessen the inventive merit in cloning the Epo gene. This position is in line with the ruling of Decision T 296/93 of 28 July 1994, point 7.4.4 (to be published in the OJ EPO) that the inventive merit of subject-matter that has been considered as non obvious cannot be lessened by the fact that the inventor was working under more favourable conditions than others.

Long probe approach

134. That a person skilled in the art would have envisaged in the late 1983 using the long probe approach, published shortly before the priority date of the patent in suit in Anderson (P3), for isolating the Epo gene with a reasonable expectation of success was the main basis for the Appellants' attack on inventive step. To support it, a series of experiments were carried out showing that working with the means published before the priority date of the patent in suit would have resulted in the provision of the Epo gene without applying inventive skill. These are the so-called "Dr Grundmann Experiments" already mentioned in respect of Article 83 EPC requirements (cf. points 81 ff *supra*).

135. The Respondents' arguments against the long probe approach based on the analysis of Prof. Lathe's Exhibits [P24, P133, P131, P134, P102, P130, P146, P25,

P85, P26, P78, P10, P72, P5, P1 (2 examples), P132, P52 and P12], provided as Figure C to "Oral 17" (page 928 of the Appeal file), are strong. Prof. Lathe's above list comprises examples of the successful application of the long probe approach, selected by an expert put forward by the Appellants. If therefore the selected examples strongly favour the Respondents' case, this cannot be attributed to any purposive selection, but can be taken as reflecting the general view in the art of how skilled persons viewed the long probe approach shortly after the priority date of the patent. None of documents of Prof. Lathe's list discloses a long probe approach for screening a genomic library precisely as taught by Anderson (P3).

136. Ullrich (P131) is concerned with the screening of a genomic DNA sequence coding for IGF-I with a single long probe (103-mer). However, the 103-mer used as a long probe was a DNA fragment coding for the B-chain of IGF-I synthesized with the intention of expressing the IGF-I protein in *E.coli* (see page 361 and Table 2b)) for the production of the IGF-I protein. This document thus does not adopt the mammalian or human codon usage as prescribed by Jaye (P64) and Anderson (P3), but rather, the *E. coli* codon usage. The above anomalous situation, which follows from the availability of the 103-mer synthesized for other purposes, can therefore not directly be compared with the problem to be solved in the present case, where it has to be decided whether the skilled person was inclined to use an unmodified long probe approach as taught by P3, for screening a genomic library for a quite large gene, having also regard to the fact that a possible failure by Prof. Ullrich with the screening process would not have

prejudiced the use of his 103-mer as insert for an *E. coli* expression system. In answering thus the question of the skilled person's readiness to adopt an unmodified Anderson's technique, the Board observes that, once document P131 has to be regarded as an anomalous case, none of the remaining 18 examples of long probe techniques discloses the use of a single probe for screening a genomic library as did Anderson. In connection with Anderson, it should be noted that the Anderson's 66-mer is not distinct from the 86-mer since it represents merely a shorter form thereof, i.e., document P3 is not a disclosure of the use of more than one long probe (see page 6840, left column, line 5). More than one probe, however, is always used in the long probes techniques disclosed by Dernyck (P24), Toole (P130), Dernyck (P25) and Abraham (P1), i.e, those documents dealing with the screening of genomic libraries. It is true that a passage bridging left and right column of page 363 of P131, relating to a personal communication of P. Seeburg, seems to suggest that a 38-mer unique probe had been used successfully for the isolation of a specific chromosomal gene, as Prof. Lathe submitted at the oral proceedings. However, no exact analysis of the technique P. Seeburg actually used is evident to the Board, so that from this statement alone the conclusion cannot be drawn that the long probe approach of Anderson (P3) would have been considered as the "key" teaching as to how to proceed if a genomic bank had to be screened, since because of the short supply of mRNA, the easier route of the cDNA library provision and screening was not available.

137. Two important trends seem to emerge from Prof. Lathe's list: (i) most of the examples deal with screening cDNAs rather than genomic DNAs and (ii) in the few examples relating to screening of genomic libraries , there is a strong tendency to avoid using solely a unique probe. In the Board's opinion the above findings (i) and (ii) are not due to a mere coincidence, but are fully in line with the common general knowledge that a genomic library is by far more complex than a cDNA one, and also confirm Prof. Ullrich's and Prof. Winnacker's statements (P154, page 10, lines 5 to 10 and P179, page 8, end of second paragraph) that the likelihood of being successful increases with the number of probes used, by minimization not only of the probe's specificity problem but also of the intron problems.

138. In view of the above, the examples of using the long probe approach do not support the Appellants' position that the skilled person would have used without modification Anderson's teaching for screening a genomic library for an Epo gene. It must be concluded that an ordinarily skilled person while considering the Anderson's disclosure as a further step in developing efficient methods for the screening of genomic libraries when looking for complex genes, would equally have hesitated long before attempting to apply the above technique in situations where, as for Epo, far less was known about the protein for which it coded than was the case for Anderson, in view of additional measures needed to minimize specificity or introns problems.

139. In connection with the question of how a skilled person viewed the Jaye-Anderson's technique in late 1983 the

Respondents' further submission on the long probe approach was based on the fact that Dr Fritsch, who was looking for the Epo gene, did not turn to this new technique despite of failure. The Appellants argue that he was prevented from doing so by the publication in January 1984 of P162 announcing the Respondents' success in cloning the Epo gene. However, the Board is not convinced by said Appellants' position in view of the fact that the Jacob sequence (P63), i.e., in essence the Epo sequence DNA of the patent in suit, was not published until 1985 and all the teams looking for the Epo gene still had the incentive to find the gene.

140. Even disregarding the Board's above conclusion based on Prof. Lathe's list, the further evidence and submissions provided by the Respondents are equally conclusive against the Appellants' line of argument that an ordinarily skilled person at the time in question would have reasonably expected to succeed in isolating the Epo gene with the Anderson technique, having regard to the following:

(i) Jaye's (P64) and Anderson's (P3) long probes were designed in the light of the known complete amino acid sequence of factor IX and BPTI, respectively and, therefore, Jaye and Anderson were able to choose areas of least degeneracy. No such amino acid sequence information, let alone said regions of least degeneracy were available from the published sequence (P121) in the case of Epo. Prof. Lathe emphasized at the oral proceedings that the long probe approach relied on the choice of codons in which possibly only 2 of 3 bases match rather than on the

selection of the most frequent codons. By this expedient, the possibility of selecting a wrong triplet was minimized and one ended up with a probe with about 80% homology. However correct Prof. Lathe's declaration may be, it cannot be disputed that the above strategy does not work in the case when one encounters a 6-fold-degenerate codon because the first two bases of the triplet are also different. This explains why Jaye (P64, page 2328), the teaching of whom the skilled person had no valid reasons to set aside in late 1983, warns that 6-fold-degenerate codons should be avoided and why Anderson chose the second half of the sequence that had only 4 highly degenerate codons. It is therefore not very likely that the skilled person would have adopted in late 1983 the guessmer technique, once he had realised that the only sequence available from P121 was far from fulfilling the requirement of least codon ambiguity (see Figure A on page 926 of the Appeal file).

(ii) Jaye used the codon usage found in sequenced cDNAs of bovine proteins secreted by the liver. In the light of this, the probe construction in the case of Epo should have been based on the human codon usage of kidney. This was not known.

(iii) Andersons' 66-mer probe was not specific. The Appellants' argument to the contrary, which relies on document P3, page 6840, left column, lines 4 to 5, according to which the bands detected by the 86-mer were also visible with the 66-mer, does not withstand a closer

scrutiny. In fact, the same passage recites that non specific background and additional faint bands were also visible with the 66-mer. And indeed Anderson refrained from using the 66-mer in the screening procedure, after it turned out to yield additional bands and high background in the Southern blots, because the additional bands would have meant additional cumbersome characterisation work (see paragraph iv *infra*).

(iv) Both Jaye and Anderson were able to characterize the putative positive clones by reference to the known full amino acid sequences of factor IX and BPTI, while in the case of Epo any means for this confirmation were missing. The Appellants argued that Examples 3 and 5 of the patent itself, disclosing the simple sequencing of the positive clone λhE1, showed that there was no difficulty in characterizing the positive clones. According to the Appellants, Dr Grundmann was able to select the positives in the light of Sue's (P121) sequence. The Board finds these arguments in contrast to the patent's teachings, from where it is clear that one cannot be sure of having picked up the right gene until the positive result is confirmed by other investigations such as heteroduplex formation with the monkey cDNA (page 17, line 9), expression in COS cells (Examples 6 and 7A), analysis of all possible reading frames (page 14, line 59) and study of polypeptide sequence homology between human and monkey Epo (Table VII). None of these additional tests are

necessary if the complete amino acid sequence is known.

141. The Board agrees with Prof. Davidson's view (P160, Section 14) that due to the limited knowledge of the amino acid sequence of Epo, mere sequencing of positive clones left the skilled person uncertain as to whether the entire gene had been cloned, since certainty was confined to the DNA segment spanning the base sequence of the probe. A further support for the Board's above view is Dr Powell's statement on page 4 of his declaration (P297) that he confirmed the Epo gene sequence of his positives with a probe designed in the light of the published Epo DNA sequence of Epo (P63) rather than with very complex and cumbersome methods available in 1983. Certainly, once a genomic sequence has been published, nobody would turn to more cumbersome methods of checking. Otherwise, while DNA sequencing gives useful information about the amino acid sequence, it does not necessarily provide unambiguous evidence in confirming that a gene looked for has been actually picked up.

142. Finally, Dr Grundmann's experiments which are supposed to prove that working merely according to teachings of the prior art would in an obvious manner result in the invention, have to be examined as to whether they rely on advantages which were not available to the skilled person in 1983. The following analysis will clarify the situation:

(i) The first assumption for carrying out these experiments must be that the information that the Grantham tables (P50) have enough

correlation to the Epo codon preference and the assumption that no unusual codons underlie the rare protein Epo. While the Board accepts that it was known that highly expressed genes comprise common codons, the reverse conclusion, i.e., genes whose expression product is low comprise rare codons, is not necessarily true, in view of the cell's alternative regulation systems. Nevertheless, it cannot be disputed that the common belief in late 1983 that, at least insofar as *E. coli* was concerned, there was a correlation between unusual codon usage and rarity of the protein, increased the skilled person's uncertainty as to which should have been the Epo optimal codon choice.

(ii) A second assumption must be that the full Epo gene was present in the Lawn genomic library (P79). The Appellants countered by relying upon the footnote to Figure 1 of P79 showing that a Lawn gene bank has 99% probability of containing any sequence present in the genome. However, the Board notes that the 99% probability relates to the definition of a complete gene bank and genomic banks are not necessarily complete. That it cannot be taken as granted that a given library will contain the sought gene, finds support in other research groups' (including Anderson) failure in recloning the BPTI gene in 1986, because of their use of a λ Charon 30A genomic bovine library instead of the Karn bovine library used in P3 (see annex L to P160, page 7115, right column). Thus the information

derivable from the patent that one would have found the entire Epo gene in a Lawn gene bank rather than in another genomic bank represents useful information not available at the priority date that increases the likelihood of success.

(iii) Further useful information not available at the priority date would be that there are only two mistakes in the Sue (P121) sequence, and that it did not span an intron. While this was available to Dr Grundmann when considering the undertaking of the long probe approach, it is questionable whether in the absence of such information, a skilled person in late 1983 would have had any confidence of success.

(iv) The choice of the hybridization conditions is critical. In his second and third experiments (P253 and P252), in an attempt to overcome the Respondents' criticism to the hybridization conditions selected in the first experiment (P231), Dr Grundmann used the same hybridization temperature as Anderson (65°C). In the first experiment Dr Grundmann chose a hybridization temperature resulting from averaging Jaye's hybridization temperature (calculated from the Thomas and Dancis formula, see P'267) with the Anderson's. The Board is of the opinion that averaging a theoretical value and an empirical one is questionable. However, the above hybridization temperature of 65°C used in Dr Grundmann's further experiments is likewise questionable. In fact, a careful reading of Anderson (P3, paragraph bridging page 6839 and

6840) shows that the Anderson's approach to establishing the hybridization temperature, unlike the Jaye's, is an empirical one, i.e., it is obtained by first adjusting in a Southern blot test the hybridization and washing temperatures until several specific bands are clearly visible over the background noise, then the plaque hybridization is carried out under the same conditions as used for the Southern blots. The Anderson's hybridization temperatures turned out to be 65°C for the 86-mer and 60°C for the 66-mer. Dr Grundmann's adoption of the Anderson's temperature of 65°C chosen to overcome the Respondents' criticism, might possibly not reflect a true working according to the teachings of the prior art, since the hybridization temperature of a probe, depending mainly on the probe's length and GC content, should have been also empirically established and it is unlikely that it would have coincided with the temperature of 65°C found by Anderson in view of the differences between the BPTI and Epo probes. In conclusion, Dr Grundmann could not exactly follow the Anderson's teachings and thus the Board is left with the uncertainty of whether Dr Grundmann's probe would have been specific at the actual hybridization temperature which according to Anderson is to be determined by a stated experimental procedure. The use of a correct hybridization temperature is one of the most critical factors that contribute to the success of a guessmer approach and there seems to be no escape from this dilemma than to try the working conditions for each and every

isolation of a gene. Working according to the precise recipe of a particular piece of prior art relating to another gene to show lack of inventive step in this particular field of genetic engineering is of only limited value, because of the unique characteristic of each and every gene which make extrapolations highly speculative. The Board can only conclude that the approach of combining the two teachings of Anderson (P3) and Sue (P121) to arrive at a solution to the problem solved by the present invention is obvious only in hindsight, but would not have been obvious to the skilled person at the priority date.

(v) The Appellants (see e.g, Prof. Lathe's Declaration (P180, point 11)) presented arguments before the Opposition Division to the effect that a long probe "guessmer" could have been designed and used not only according to the teachings of Anderson (P3) but also in the light of Jaye (P64). However, after Prof. Davidson (P160) outlined that the Jaye's instructions were partially incorrect owing to some erroneous assumptions and to the use of a flawed formula to calculate the hybridization temperature (P160, Sections 19 and 31, respectively), the Appellants withdrew reliance on the Jaye's paper throughout the opposition and appeal proceedings. The Board is nevertheless thus left with the doubt of whether the skilled person might not have been misled by these teachings.

143. In conclusion, on the evidence and arguments put to the Board, the Appellants have not made out a plausible case that a person skilled in the art would have arrived at something falling within the Claim 1 to the DNA without this involving an inventive step having regard to the state of the art. Claims 2 to 11 are dependent on Claim 1, Claims 12 to 16 are claims directed to cells incorporating DNA as in Claim 1 (or claims dependent thereon), Claim 17 is a claim to a vector incorporating the DNA according to Claim 1 (or claims dependent thereon), and Claim 18 is a claim to a cell transformed or transfected with a vector of Claim 17. Accordingly once an inventive step has been acknowledged for Claims 1, it must be acknowledged for these claims as well.

Inventive step (Claims 19 to 25 to polypeptides)

144. Claim 19 is directed to a recombinant polypeptide having part or all of the primary structural conformation of human or monkey erythropoietin as set forth in Table VI or Table V ...*which has higher molecular weight by SDS-PAGE from erythropoietin isolated from urinary sources*. This last feature distinguishes it from Epo obtained by the only known process for obtaining Epo, urinary extraction, or any modification of this process of urinary extraction. In relation to the product of this urinary extraction process, the problem to be solved can be stated as the provision of an alternative form of Epo. This problem is solved according to the present invention by the recombinant process of Claim 1, and expression in CHO or COS cells to produce a product with higher molecular weight. While in theory the way to solve this problem

was obviously to use a recombinant route, the discussion above concerning Claim 1, makes clear that this route involved an inventive step over the prior art. As, on the evidence, the provision of such a higher molecular weight Epo, was only possible by solving the problem of developing a recombinant route, an inventive step can here be acknowledged for the provision of the alternative product.

145. Claims 20 to 25 are directly or indirectly dependent on Claim 19 so there is no need to consider their novelty or the presence of an inventive step separately from that of Claim 19.

Novelty and Inventive step (Claims 26 to 29)

146. Claim 26 is directed to a polypeptide product of the expression in a eucaryotic host cell of a DNA sequence according to any of Claims 1, 2, 3, 5, 6 and 7. Claims 2, 3, 5, 6 and 7 are directly or indirectly dependant on Claim 1. If a product is not capable of being made with a DNA according to Claim 1, it does not fall under Claim 26, so no issue under Article 83 EPC separate from the ones already considered in relation to Claim 1 arises in relation to Claim 26. Further on the evidence presented, it appears that expression in a eucaryotic host cell will ensure glycosylation of the product, thus distinguishing it from the aglyco Epo of the prior art. Thus in contrast to the situation for Claim 19 of auxiliary request 2 considered in points 31 to 41 *supra*, the Board is on the evidence prepared to presume that the limitation to the polypeptide being a product makable using the DNA of Claim 1, is a technical feature that ensures that it has a

glycosylation pattern different from the known u-Epo, and that the existence of novelty and inventive step for the DNA for Claim 1, allows the Board to find novelty and an inventive step also for the subject-matter of Claim 26.

147. Claim 27 is directed to a process for production of a peptide characterized by culturing under suitable conditions a procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to any of Claims 1, 2, 3, 5, 6 and 7. As these sequences have been found novel and to involve an inventive step, this claim to their use must also be considered to be novel and to involve an inventive step. The same applies to process Claims 28 and 29 dependent thereon. The fact that one product made thereby when a procaryotic cell is used is aglyco Epo, which is not novel, cannot deprive such process claims of novelty.

Novelty and Inventive step (Claims 30 and 31)

148. Claim 30 is directed to a pharmaceutical composition comprising the polypeptide product made by the process of Claim 27, 28 or 29. No evidence was presented that the minimal quantities of u-Epo available from the prior art were available in a form suitable as a pharmaceutical, and this is inherently unlikely. Accordingly the Board considers this claim to be to novel subject matter. To make a pharmaceutical available would once again require the problem of finding a recombinant route to be solved, as was done with the provision of the DNA of Claim 1. On this basis

inventive step can also be acknowledged for Claim 30 and Claim 31 dependent thereon.

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 Claims 1 to 31 of the eleventh auxiliary request submitted on 22 September during the oral proceedings.

The Registrar: The Chairwoman:

L. McGarry U. Kinkeldey

ANNEX I

GLOSSARY AND LIST OF ACRONYMS

Epo:	erythropoietin
u-Epo:	human urinary erythropoietin
r-Epo:	recombinant human erythropoietin
g-DNA:	genomic DNA
mRNA:	messenger RNA
cDNA:	complementary DNA
m.w.:	molecular weight
IEF:	isoelectric focusing
SDS-PAGE:	sodium dodecyl sulphate polyacrylamide gel electrophoresis
HPLC:	high-pressure (performance) liquid chromatography
RP-HPLC:	reversed phase-HPLC.
ORF:	open reading frame: this contains a series of triplets coding for amino acids without any termination codons; sequence is (potentially) translatable into protein. (Lewin, Genes V, Glossary)
RIA:	radioimmunoassay

ELISA: enzyme-linked immunosorbent assay

ANNEX II

CLAIMS

Claims 1 and 2 as granted, and of all requests read:

1. A DNA sequence for use in securing expression in a procaryotic or eucaryotic host cell of a polypeptide product having at least part of the primary structural confirmation [*sic*] of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin [*sic*] synthesis or iron uptake, said DNA sequence selected from the group consisting of:

   (a) the DNA sequences set out in Tables V and VI or their complementary strands;

   (b) DNA sequences which hybridize under stringent conditions to the protein coding regions of the DNA sequences defined in (a) or fragments thereof; and

   (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) and (b).

2. A DNA sequence according to Claim 1 encoding human erythropoietin.

Claim 3 of the main request and auxiliary requests 1, 4, 7 and 10 reads:

3. A cDNA sequence according to Claim 1 or 2.

Claim 19 of auxiliary request 2 and Claim 17 of auxiliary request 3 each read:

19. A recombinant polypeptide having part or all of the primary structural conformation of human or monkey erythropoietin as set forth in Table VI or Table V or any allelic variant or derivative thereof possessing the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin synthesis or iron uptake and characterized by being the product of eucaryotic expression of an exogenous DNA sequence.

Claim 19 of auxiliary request 5 and Claim 17 of auxiliary request 6 each read (differences from Claim 19 of auxiliary request 2 shown in italics):

19. A recombinant polypeptide having part or all of the primary structural conformation of human or monkey erythropoietin as set forth in Table VI or Table V or any allelic variant or derivative thereof possessing the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin synthesis or iron uptake and characterized by being the product of eucaryotic expression of an exogenous DNA sequence *and not being identical to erythropoietin isolated from urinary sources*.

Claim 19 of auxiliary request 8 and Claim 17 of auxiliary request 9 each read (differences from Claim 19 of auxiliary request 2 shown in italics):

19. A recombinant glycoprotein polypeptide having part or all of the primary structural conformation of human or monkey erythropoietin as set forth in Table VI or Table V or any allelic variant or derivative thereof possessing the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin synthesis or iron uptake and characterized by being the product of eucaryotic expression of an exogenous DNA sequence *and having an average carbohydrate composition which differs from that of human erythropoietin isolated from urinary sources*.

Claims 3 to 31 of auxiliary request 11 read :

3. A cDNA sequence according to Claim 1 being a monkey species erythropoietin coding DNA sequence.

4. A DNA sequence according to Claim 3 and including the protein coding region set forth in Table V.

5. A genomic DNA sequence according to Claim 1 or 2.

6. A human species erythropoietin coding DNA sequence according to Claim 5.

7. A DNA sequence according to Claim 6 and including the protein coding region set forth in Table VI.

8. A DNA sequence according to Claim 1 or 2, covalently associated with a detectable label substance.

9. A DNA sequence according to Claim 8, wherein the detectable label is a radiolabel.

10. A single-strand DNA sequence according to Claim 8 or 9.

11. A DNA sequence according to Claim 1, coding for [Phe^{15}]hEPO, [Phe^{49}]hEPO, [Phe^{145}]hEPO, [His^{7}]hEPO, [Asn^{2} des-Pro^{2} through Ile^{6}]hEPO, [des-Thr^{163} through Arg^{166}]hEPO, or[$\triangle$27-55]hEPO.

12. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to any one of Claims 1, 2, 3, 6, 7 and 8, in a manner allowing the host cell to express said polypeptide product.

13. A transformed or transfected host cell according to Claim 12 which host cell is capable of glycosylating said polypeptide.

14. A transformed or transfected mammalian host cell according to Claim 13.

15. A transformed or transfected COS cell according to Claim 13.

16. A transformed or transfected CHO cell according to Claim 13.

17. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to any one of Claims 1, 2, 3, 5, 6, 7, or 11.

18. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to Claim 17.

19. A recombinant polypeptide having part or all of the primary structural conformation of human or monkey erythropoietin as set forth in Table VI or Table V or any allelic variant or derivative thereof possessing the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells to increase hemoglobin synthesis or iron uptake and characterized by being the product of eucaryotic expression of an exogenous DNA sequence *and which has higher molecular weight by SDS-PAGE from erythropoietin isolated from urinary sources*.

(differences between this Claim 19 and Claim 19 of auxiliary request 2 are shown in italics)

20. A glycoprotein polypeptide according to Claim 19 having an average carbohydrate composition which differs from that of human erythropoietin isolated from urinary sources.

21. A polypeptide according to Claim 19 or 20 wherein the exogenous sequence is a cDNA sequence.

22. A polypeptide according to Claim 19 or 20 wherein the exogenous DNA sequence is a genomic DNA sequence.

23. A polypeptide according to Claim 19 or 20 wherein the exogenous DNA sequence is carried on an autonomously replicating circular DNA plasmid or viral vector.

24. A polypeptide according to any one of Claims 19 to 23 further characterized by being covalently associated with a detectable label substance.

25. A polypeptide according to Claim 24, wherein said detectable label is a radiolabel.

26. A polypeptide product of the expression in a eucaryotic host cell of a DNA sequence according to any of Claims 1, 2, 3, 5, 6 and 7.

27. A process for production of a polypeptide having at least part of the primary structural conformation of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin synthesis or iron uptake, which process is characterized by culturing under suitable nutrient conditions a procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to any of Claims 1, 2, 3, 5, 6 and 7 in a manner allowing the host cell to express said polypeptide; and optionally isolating the desired polypeptide product of the expression of the DNA sequence.

28. A process according to Claim 27, characterized by culturing a host cell of any one of Claims 12 to 16.

29. A process according to Claim 27 or 28 for production of a polypeptide of any one of Claims 19 to 23 and 26.

30. A pharmaceutical composition comprising a polypeptide produced in accordance with the process of Claim 27, 28 or 29 and a pharmaceutically acceptable diluent, adjuvant or carrier.

31. A pharmaceutical composition according to Claim 30, comprising a polypeptide of any one of Claims 19 to 23 and 26.

ANNEX III

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