alleged to infringe can be said to have independent validity. If it should transpire that the Amgen parties contend for independent validity of any of the other claims, then further submissions directed to such claims may be necessary.

Insufficiency (1) - human EPO cDNA

54. The Amgen parties suggest three ways in which the 605 patent might enable the production of human EPO cDNA: (1) via a suitable tissue source (2) via cell expression and (3) by DNA synthesis. We deal with these three issues in turn, on the assumption that the claims of the 605 patent are construed to cover human EPO cDNA (and products derived from its use).

Tissue sources

55. The 605 patent presents the absence of a tissue source from which a cDNA library containing human EPO cDNA could be constructed as one of the major obstacles to cloning human EPO DNA (see p.6 line 57 – p.7 line 2). This problem had two possible solutions. A suitable source of mRNA could have been found, or another route to human EPO DNA (ie the genomic route) could have been followed. There were two alternative inventions which could have been made. The patentee chose the latter approach. His invention was to avoid the problem of the lack of a suitable source of mRNA by instead screening a human genomic library.

56. The only suggestion in the 605 patent of a suitable tissue source is human kidney (p.7 lines 11-23). As all agree, this was not practicable and would not have led to success (Brammar 1 §70 [H/1], Wall 1 §75 [F1/5], Fritsch 2 §7.2 [H/9]).

57. The Amgen parties contend that, despite the fact that the 605 patent does not suggest any tissue source from which a cDNA library containing human EPO cDNA could be made, nonetheless human EPO cDNA is enabled. They suggest that the skilled worker could design a probe based on the Table VI sequence and go hunting for a tissue source (Wall 1 §111 at end).

58. The Roche parties contend that this does not amount to enablement. On the contrary, it is asking the skilled person to embark on a research project.

59. In any event, there is no reason to believe that the skilled person would be successful if he did embark on such a research project. The only tissue source from which human EPO cDNA has ever been isolated is 20 week old fetal liver (Fritsch 2 §7.7). Further, the 20 week old fetal liver library from which GI succeeded in isolating human EPO cDNA was a library containing a very large number of clones (approaching 1 million), with a success rate of 1 clone containing EPO cDNA sequence per 300,000 screened (comparable to the frequency of occurrence in a genomic library) (Fritsch 2 §3.8). As Dr Fritsch says (Fritsch 2 §7.11) GI's success in isolating human EPO cDNA was down to his luck in having the right tissue source and a good library made from that tissue source.

60. The Amgen parties rely on certain papers (Wall 2 §7 [F3/5]). But, as Dr Fritsch says (Fritsch 2 §7.3-7.7), these papers were inconclusive and did not indicate that fetal liver would yield enough EPO mRNA to enable production of a cDNA library containing EPO cDNA. It was likely that, as in the adult kidney, EPO mRNA was only produced in the fetal liver in response to certain physiological conditions. Nor was it known whether the gene expressed in fetal liver was the same as that expressed in adult kidney, nor whether expression would be time-dependent (as, it is now believed, it is). These papers do not point towards the use of 20 week old fetal liver. What is more, they were not cited in the 605 patent, so there is nothing to guide the skilled reader to them.

61. The key to obtaining human EPO cDNA was not the Table VI sequence, but the 20 week old fetal liver and the library made from it. Human EPO cDNA could have been isolated from that library with mixed oligo probes without any need for the Table VI sequence (Fritsch 2 §7.12-7.13, see also Brammar 1 §§60 & 66).

62. It should be noted that the 605 patent does describe in some detail a method for obtaining a monkey EPO cDNA clone. This method involved treating monkeys with phenylhydrazine hydrochloride to make them anaemic and then harvesting their kidneys. This induced anaemia led to an overproduction of EPO mRNA from which a cDNA library could be made. This method could obviously not be used to obtain human EPO cDNA.

Cell expression

63. The Amgen parties rely on the passing reference at the end of example 5 of the 605 patent (p.25 lines 17-20), where the patentee is comparing the monkey and human EPO amino acid sequences. He has deduced the monkey sequence from the monkey cDNA and the human sequence by comparison of the human genomic sequence with the monkey cDNA and knowledge of consensus splice donor and acceptor sites. He notes that there is an extra lysine in the deduced human sequence. He says that its presence in the human sequence can be verified by some sequencing of a cDNA clone prepared from mRNA isolated from COS cells transfected with the human genomic clone.

64. This brief reference would not be understood as indicating that an authentic human cDNA had been produced. If it had been, the inventor would have used its sequence (instead of that of the monkey cDNA) to confirm the human EPO amino acid sequence and would have disclosed the sequence in the 605 patent (Brammar 1 §§72-74 [H/1]). Instead, the skilled reader would understand that the inventor had used this approach merely to obtain a sufficient part of the human EPO cDNA sequence to verify the presence of the lysine residue.

65. There is no suggestion in the 605 patent that this is a route to a human EPO cDNA that could be used to express biologically active recombinant EPO. In fact, the specification at p.11 lines 47-49 describes example 5 as *"directed to DNA sequencing of a positive genomic clone and the generation of human EPO polypeptide amino acid sequence information including a comparison thereof to the monkey EPO sequence information."*

66. Prof. Wall says that the use of COS cells to produce mRNA from which cDNA could be made was a well-known technique in 1983 and relies on a number of papers in support of that suggestion (Wall 1 §§109 & 111 [F1/5], Wall 2 §§15-19 [F3/5]). Prof. Brammar disagrees – he says it was not an accepted route (Brammar 2 §17 [H/6]). There is also a dispute between Profs. Wall and Brammar regarding the level of artefacts that would be produced by the use of such a technique (Brammar 1 §§75-79 [H/1], Wall 2 §§20-25 [F3/5]). These disputes will have to be resolved in cross-examination.

67. Two points are, however, worth noting at this stage. First, the later paper by Wojchowski *et al.* (1987) [L5a/166] shows what can go wrong when this technique is employed (Brammar 1 §§80-85). Secondly, the cell expression technique was not one which was included even in the 2nd edition of the Maniatis manual (published in 1989) or taught on the Cold Spring Harbor Molecular Cloning courses in 1980-1983 (Fritsch 2 §8.3 [H/9]).

Gene synthesis

68. The Amgen parties assert that human EPO cDNA could be made by gene synthesis using the Table VI sequence. This assertion is misconceived for at least the following reasons.

69. First, the 605 patent clearly distinguishes between cDNA and synthetic DNA – see e.g. p.3 lines 12-15 (Gassen 1 §§7-10 [H/3]). This is an entirely proper distinction, not only having regard to the different processes by which the two are made but also to the fact that the two are different products with different sequences. There is no suggestion in the patent that this route could be used to make a human EPO cDNA.

70. Secondly, manufacture of the coding region of a synthetic EPO gene would require changes to be made from the sequence of human EPO cDNA. Such changes arise from the way in which synthetic DNA is designed and constructed. The changes can be more or less extensive depending on the design strategy, but there are always some. Thus any synthetic DNA sequence cannot

be the same as the cDNA. For a discussion of this topic see Gassen 1 §§29-39 and Gassen 2 §§15-17 [H/8]. Dr Gait proposes a sequence that involves only two changes (Gait 1 §§31-38 [F1/3] & Annex 4 [G1/12]) but this is just paper chemistry as Dr Gait does not indicate how the sequence can be made practically (Gassen 2 §§14-18).

71. Thirdly, even by the end of 1984, the ability to synthesise an expressible gene of 500 base pairs or more (as required for the coding region of EPO) was restricted to a few specialist groups and was a major research project. There is a dispute between Prof. Gassen (Gassen 1 §§13-28, Gassen 2 §§3-11) and Dr Gait (Gait 1 §§9-19 & 25-30, Gait 2 §§3-11 [F3/3]) as to quite how difficult, lengthy and unpredictable the exercise would have been. This dispute will have to be resolved in cross-examination.

72. Fourthly, by the end of 1984 no one had expressed a synthetic gene in a mammalian cell (Gassen 1 §41, Gassen 2 §§19-20). The work required of the skilled person by the Amgen parties – synthesis of a 500+ base pair gene and expression in a mammalian cell – would have been considered pioneering even for a specialist team in 1984 (Gassen 2 §21). The 605 patent describes an attempt to express the synthetic genes in *E.coli* and yeast. Neither of these host cells would produce properly glycosylated human EPO.

Summary

73. In summary, none of the proposed routes to human cDNA is enabling. But even if one of them is, any claims of the 605 patent claiming human EPO cDNA (or which claim a product produced by the expression of a human EPO cDNA) are still invalid for insufficiency, as there are routes to human EPO cDNA which are not enabled by the 605 patent and/or owe nothing to the patentee's invention. This is particularly true in respect of tissue sources which would have been the route of choice had a tissue source been made available by the 605 patent, which it was not.

Insufficiency (2) – hybridisation, stringency and degeneracy

74. Part (b) of claim 1 covers DNA sequences for the use set out in the preamble which are:

> *"DNA sequences which hybridize under stringent conditions to the protein coding regions of [the DNA sequences set out in Tables V and VI or their complementary strands] or fragments thereof"*

75. This is not a properly defined and circumscribed class. The skilled man is left to devise the conditions to be used in the hybridisation test, as no level of stringency is prescribed. One of the problems for the skilled person is that the conditions under which a given DNA sequence will hybridise to another depends on the degree of homology between the two, the length of the two sequences and the G/C content of the sequences. So the conditions which can be withstood while still maintaining hybridisation vary from one pair of sequences to another. But the test cannot be a self-fulfilling one – devise conditions so that you get hybridisation – as the test is supposed to be a means of defining the scope of the invention and if the test is self-fulfilling it has no limiting effect. So there should be some defined "stringent conditions", yet there are none. Merely to test on a trial and error basis will not do (see *Novo Nordisk v. DSM*, Neuberger J. 21/12/00 at §177). As in *Novo Nordisk*, the scope of the claim will vary depending on the judgment of the person conducting the work.

76. Worse still, a sequence falls within part (b) if it hybridises (to some undefined extent) to the protein coding regions of the Table VI sequence *or fragments of such regions*. In other words, hybridisation to any part (large or small) of the protein coding parts of the Table VI sequence is enough. All such sequences must be tried, and tried under conditions which are undefined, to see whether there is some (undefined) degree of hybridisation.

77. The same criticisms (and more) can be made of part (c):

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

78. Here, it should be noted, it is not even said that the conditions should be "stringent" (whatever those may be). So what conditions should a skilled person choose to see whether his sequence hybridises (to some undefined extent)? The less stringent the conditions chosen, the more sequences will hybridise. How is the skilled person to know if he infringes?

79. But the matter does not end there. What is required are sequences which *but for the degeneracy of the genetic code* would hybridise to either a part (a) or a part (b) sequence. Take part (a) sequences first. Here, the skilled person has to work out whether his sequence would, but for the degeneracy of the genetic code, hybridise under undefined conditions to e.g. the Table VI sequence. So the sequence he has could be completely different to the Table VI sequence. He can notionally mutate it into a range of sequences which are closer to Table VI using the degeneracy of the genetic code. But he cannot then do a test, as he does not actually have any of the notionally mutated sequences. So what is he to do – guess whether any of them would hybridise under undefined conditions? This of course assumes that he also has a clone with the Table VI sequence – on Prof. Wall's evidence, this alone could take several months to obtain.

80. Things are even worse if he is trying to tell whether his sequence would hybridise (under undefined conditions, to an undefined extent) to a part (b) sequence. Part (b) encompasses a whole range of sequences itself. The skilled person has notionally to mutate his sequence, using the degeneracy of the genetic code, into a whole range of other sequences which might hybridise under undefined conditions to one of the sequences which hybridise under "stringent" conditions to the protein coding regions of part (a) sequences or fragments thereof. And then guess.

81. In all the above, we have postulated that the skilled person is given a sequence and wants to know if it infringes. But what if he simply wants to isolate or produce a sequence (either within or without the claim)? How does he know what is within the scope of the invention and what is not? The patent provides him with no means of reliably identifying or designing such a sequence.

82. While parts (b) and (c) are not in precisely the same form as the offending claims in *Novo Nordisk v. DSM*, it is submitted that, by parity of reasoning, claim 1 is bad for insufficiency. If anything, claim 1 is even less precise than the corresponding claim in *Novo Nordisk*.

83. The same criticisms apply to (dependent) claim 2. Claim 2 is to a claim 1 sequence encoding human EPO. It is wholly unclear what is encompassed by the expression "human EPO" but in any event this will be a vast and indefinite class of sequences.

84. Claim 19 suffers from a similar, but distinct problem. In particular, it covers any recombinant polypeptide which has any part of the structure of monkey or human epo and any allelic variant or derivative thereof. These are limitations which are not adequately defined in the specification to remove uncertainties inherent in the mere use of the expressions.

Insufficiency (3) & (5) – undue burden of putting the teaching into practice

85. As we have mentioned above, Amgen did not deposit any source of the EPO gene or any plasmids or cell lines containing EPO DNA. That means that a skilled person wishing to implement the teaching of the 605 patent and obtain EPO DNA and then recombinant EPO must start again, isolate the EPO gene from a library, clone it into a plasmid, construct expression vectors, transfect host cells and express the gene to produce EPO. The issue for the court is whether that involves undue effort and experimentation.

Isolation of the EPO gene (Example 4)

86. The starting point is the isolation of the EPO gene from a library. The Lawn library made by the Maniatis group (which included Dr Fritsch) was an excellent library with a large number of independent clones. It had been in great demand and by 1983 the original library was exhausted. Only a less

representative amplification of the library was available. (Brammar 1 §94 [H/1], Fritsch 2 §§1.3-1.4 [H/9]).

87. The alternative was to try to make a genomic library oneself. But following the Lawn / Maniatis procedures was a daunting task that would have required many man-months of work (Brammar 1 §92). This is precisely why the original Lawn library was in such demand – it was extremely difficult to make such a representative library. Libraries could have been constructed by other methods, but the libraries would not have been the same (Brammar 1 §93). Prof. Wall's suggestion is that one could construct and screen other libraries until one was successful (Wall 1 §101 [F1/5]).

Construction and use of expression vectors (Examples 6, 7 and 10)

88. The 605 patent describes the construction of expression vectors for human EPO gDNA and their use to transfect COS and CHO cells.

89. Example 6 includes the construction of the plasmid pDSVL1. In Example 7B, EPO gDNA is inserted into that plasmid to produce the expression vector pSLVgHuEPO, which is used to transfect COS cells. The vector is also used in example 10 (where it is referred to as pDSVL-gHuEPO) to transfect CHO cells.

90. Example 7A involves the creation of plasmid pSV4SEt, the insertion of EPO gDNA into that plasmid to produce the expression vector pSVgHuEPO and its use to transfect COS cells. The vector is also used in Example 10 to transfect CHO cells. In this expression vector, expression is supposed to be driven by the endogenous EPO promoter.

91. There are numerous defects in the instructions in Examples 6 and 7, as explained by Prof. Brammar (Brammar 1 §§95-117 [H/1] & Figs. G-I in Annex 3 [I/3]). These points are addressed by Prof. Wall (Wall 1 §§115-124 [F1/5], Wall 2 §§37-50 [F3/5]). It is probably not profitable to go into the detail of the defects at this stage, though two may merit specific mention:

- In both Example 7A and Example 7B, linkers are placed immediately upstream of the start of the EPO sequence. But the sequences of these linkers are not specified. In Example 7B, the linker lies between the SV40 promoter and the EPO sequence and will be transcribed into the 5′ untranslated region of the EPO transcript, where it may affect mRNA secondary structure, splicing or translation (Brammar 1 §113). In Example 7A, the linker lies upstream of the EPO promoter, but could affect promoter activity or be transcribed if transcription initiates upstream rather than from the endogenous promoter (Brammar 1 §106). The absence of teaching as to the linker sequences is therefore significant.

- In Example 7B, an error in the EPO gDNA sequence reported in Table VI will lead to an incorrect design of another linker. The result of this is likely to be a failure of ligation. (See Brammar 1 §114, Gait 1 §§44-47 [F1/3], Brammar 2 §§38-40 [H/6].)

92. Prof. Brammar's conclusion is that, given the defects in the instructions, it is highly unlikely that the plasmids and vectors described in the Examples could be recreated and that while one could create plasmids and vectors with equivalent functionality, that would involve a considerable amount of work, placing the skilled person trying to express the EPO gene in the same position as the patentee was (Brammar 1 §§99-100, 107-108, 116-177 & 120).

93. Prof. Wall estimates that it would take two months to create a genomic library, 17 weeks thereafter to obtain CHO cells capable of expressing EPO and a further 11 weeks to produce EPO (Wall 2 §52 & Annex 6 [G3/13]). If a deposit of a transfected CHO cell had been made then, even on Prof. Wall's estimate, about 6 months' effort and experimentation would have been avoided.

94. The Roche parties submit that the combination of the failure to deposit and the defects in the instructions mean that undue effort and experimentation is required to perform the invention and the specification is insufficient.

Insufficiency (6) – higher molecular weight by SDS-PAGE

95. The question of whether or not claim 19 should be construed so as to exclude polypeptides made using human cDNA has been considered above. However, further issues on construction arise which can best be dealt with together with the question of sufficiency.

96. Claim 19 requires the recombinant polypeptide to have, inter alia, "higher molecular weight by SDS-PAGE from erythropoietin isolated from urinary sources", while claim 20 requires it, in addition, to have "an average carbohydrate composition which differs from that of human erythropoietin isolated from urinary sources".

97. The identified feature of claim 19 was introduced by amendment before the TBA. The TBA held that claim 19 without that feature was not novel, as there was no reliable way of distinguishing uEPO from rEPO (§§31-41 of the TBA decision of 21/11/94 [M/1]). Nor did the feature of claim 20 improve matters (§§49-53 of the decision). The TBA accepted that claim 19 as amended was novel, but only on the basis that the rEPO the subject of the claim displayed a higher molecular weight by SDS-PAGE than any uEPO made available to the public (§119 of the decision).

98. Claims 19 and 20 are founded upon the passage at p.31 lines 10-22 of the 605 patent. This refers to comparisons between COS and CHO produced rEPO and human urinary EPO isolates. The particular experiments described refer to the comparison with a "cooled [*sic*, pooled] source human urinary extract". Nowhere is it stated how the human urinary EPO isolates have been obtained and isolated.

99. The experiments described are said to show that:

- the CHO-produced EPO had a "somewhat higher" molecular weight than the COS-produced EPO, which was "slightly larger" than the urinary extract;

- when sialic acid was removed using neuraminidase, the COS and CHO products were of "approximately equal" molecular weight, but both were "larger" than the asialo urinary extract;
- when Endo F was used (to remove N glycans), the CHO cell product and the urinary extract had "essentially identical" molecular weight.

100. The Roche parties submit that a skilled person reading this passage, and seeing that all products were described as "somewhat heterogeneous", would understand that the differences in migration between the CHO, COS and urinary products were sufficiently substantial to allow the assignment of different molecular weights. By contrast, the COS and CHO products after treatment with neuraminidase had mobilities that were different, but not sufficiently so to allow assignment of different molecular weights. (See Clausen 1 §§69-72 [H/2].)

101. This would be supported by the statement at line 19-22 that the products had "different average carbohydrate composition". Given the errors involved in carbohydrate composition analysis, there would have to be a significant difference in analysis results (and hence a substantial difference in carbohydrate composition) before one would claim this.

102. The skilled reader would not be surprised to be told that there were significant differences between urinary EPOs and recombinant ones, given that the recombinant EPOs were being expressed in cells which were different in tissue and species origin from those producing the native protein.

103. It is also notable that the 605 patent does not identify the method by which the "pooled source human urinary extract" was produced, nor the method by which the other "human urinary EPO isolates" were produced. Nor, consistently with this, does it indicate that different results were obtained with the other "human urinary EPO isolates". The message is that it does not matter what urinary EPO is used as a comparator – the rEPO will always have a higher molecular weight by SDS-PAGE. This is reflected in the claim, in which no particular urinary EPO is identified – the rEPO has higher molecular weight than any uEPO that can be isolated from urinary sources. The patent, in effect, indicates that rEPOs

and uEPOs can be put into two different classes which can be reliably distinguished by their differing molecular weights when compared by SDS-PAGE.

104. Thus the proper construction of claim 19 is that (a) "EPO isolated from urinary sources" can be any EPO isolated from any urine by any method and (b) "higher molecular weight by SDS-PAGE" means that there must be a sufficient difference in mobility on the gel so as to enable the skilled worker to ascribe a different molecular weight to the recombinant glycoprotein.

105. Note that beyond this the specification does not assist the skilled person in where or how to draw the line between what is and what is not "higher molecular weight".

106. It is anticipated from the Amgen parties' evidence that it may be suggested that the source of the uEPO must be a pooled source. There is nothing to indicate that this is a requirement, either in the description or in the claim. It may be that it is convenient to use a pooled source, but if a suitable single individual source is available, there is no reason not to use it as a comparator. Indeed, as will be seen, that is what Amgen did.

107. It is also anticipated that the Amgen parties may suggest that the uEPO has to be purified using the Miyake process. Again, there is no basis for this. The 605 patent does not even say that the Miyake process was used to purify the samples used as comparators. Further, it points to other processes, most notably the Yanagawa one, which can be used to isolate EPO from urinary sources (p. 6 lines 8-18 & 49-50). Sir John Walker accepts that this was a suitable alternative to the Miyake process [Walker 1 §28 [F1/4], Walker 2 §2 [F3/4]). Indeed, there is nothing to suggest to the skilled person that he need stick to any particular purification scheme in order to obtain a uEPO with the required mobility on SDS-PAGE. The point made by the 605 patent is that there is something about rEPOs as a class which distinguishes them from uEPOs.

108. However, if there is substance in the contention that Miyake must be used, then the skilled person is faced with the prospect of collecting large quantities of urine and embarking on the lengthy and complex Miyake process before he is able to compare his rEPO with a uEPO standard. This amounts to undue burden.

109. Where a monopoly is to be defined by reference to a difference between the inventive composition and a known standard, it is encumbent on the patentee sufficiently to identify the standard and the basis of assessment of the difference. The 605 patent fails in both these respects:

- if it is important that a particular uEPO preparation be used as a comparator, the patent does not disclose what that preparation is, nor how to obtain it;
- the means by which the uEPO is to be purified is not specified – this is important because the purification method can affect the migration of the uEPO sample;
- the basis on which "differences" in molecular weight are to be assessed is not specified;
- if rEPO produced according to the teaching of the patent *can* have a higher molecular weight by SDS-PAGE than EPO isolated from urinary sources, then the patent does not contain sufficient teaching as to the circumstances necessary to obtain such an rEPO – it merely suggests expressing in COS or CHO cells.

110. The Roche parties had regarded it as being plain that the term "carbohydrate composition" in the specification and in claim 20 referred to the proportions of the monosaccharides present on the EPO molecule. It now seems (see Cummings 2 §72 [F3/2]) that the Amgen parties may contend that a difference in average carbohydrate composition can be any difference in glycosylation. If that is so, then the specification does not identify the kind of differences which are contemplated, the methods which are to be used to investigate whether or not such differences exist or how a person skilled in the art is to assess whether differences of the type contemplated are present.

Insufficiency (7) - *Biogen* insufficiencies

111. This is the ground of objection that the scope of the claims is not commensurate with the technical contribution made by the disclosure in the specification.

112. In the context of the present case if, as the Roche parties contend, the breadth of the inventive contribution does not extend to any enablement of a human cDNA route, and if the scope of the claims extends to cover this route, then that scope exceeds the technical contribution made by the disclosure in the specification (see Lord Hoffman in *Biogen* at 51-52).

113. Equally, for the reasons given above, if, for example, this Court was minded to hold that the synthetic route to the relevant DNA was enabled, it would still be the case that the cDNA route from a tissue source was not. Accordingly even at this level of generality the claims would not be commensurate with the technical contribution and would be insufficient.

INFRINGEMENT

Claims 26, 27 and 28-31 (dependent on claim 1)

114. The EPO cDNA of Roche which is alleged to infringe is set out at Annex 4 to Prof. Wall's first report [G1/12]. In §129 of his report [F1/5] he draws attention to the (almost) complete identity of that sequence with the corresponding protein coding region in Table VI.

115. If which, for the reasons given above under sufficiency, is not admitted, the words "hybridize under stringent conditions" can be given a definite meaning, then whether or not there is infringement on the basis that the Roche parties' sequence falls within part (b) of claim 1 would depend upon the meaning to be given to those words.

116. However it appears from §130 of Prof. Wall's first report that the Amgen parties may be seeking to argue a different point of infringement namely that,

purposively construed, the Roche parties' sequence falls within part (a) of claim 1. This is legally a misguided exercise. Claim 1 is a single claim. It is not three claims. If and insofar as any part of claim 1 is held to be insufficient then the whole claim is insufficient.

117. There is not before the court in this action a freestanding independent claim formed only of claim 1(a). The Court therefore does not have to construe that part of the claim alone in the context of this action. No question arises as to the scope on a purposive construction of a notional claim in the form of claim 1(a). The draftsman of the specification has chosen to define the penumbra around part (a) by reference to parts (b) and (c). The Court does not have to undertake any separate exercise.

Claim 19 (and dependent claims 20, 21, 23 and 29-31)

118. The Roche parties submit that (a) infringement has not been established and (b) the questions raised on infringement serve to emphasise that the specification is insufficient:

- on its proper construction, claim 19 requires a difference in mobility on SDS-PAGE gels which is greater than any shown in the Amgen parties' experiments;

- the kinds of differences purportedly observed in the Amgen parties' experiments and said by Prof. Cummings to demonstrate infringement are of the same order of magnitude as differences which Prof. Cummings now sees in gels which were said by many contemporaneous authors (including Amgen authors) to show that uEPO and rEPO migrated identically – in other words, Prof. Cummings is applying more rigorous standards and the patent does not teach that his standard (whatever it is) is the one to be adopted;

- further, the Amgen parties' experiments do not prove infringement because the comparator uEPO used is just one uEPO obtained from a particular source and produced by the use of a particular purification procedure;

- the uEPO used in the Amgen parties' experiments has not been shown to be representative of all uEPOs and experiments reported in scientific papers and experiments conducted internally by Amgen scientists show that the migration of uEPO preparations on a SDS-PAGE gels is variable, depending on the source and purification method.

For Amgen's experiments, papers and submissions to the regulatory authorities see Clausen 1 §§93-113 & 128-136 [H/2]. For other papers on uEPO produced by different processes see Clausen 1 §§80-92 & 114-127. Also see Clausen 2 [H/7].

ADDED MATTER

The law

119. As with insufficiency, it is not proposed to recite the law in detail since this court has recently considered it in the *Novo Nordisk* case. The law is as set out in *Bonzel v. Intervention (No. 3)* [1991] RPC 553 at 573-574. Matter will be added unless the material in the specification as granted is clearly and unambiguously disclosed in the application either explicitly or implicitly.

The facts

120. The plea is contained in paragraph 4 of the Particulars of Objections [B1/5]. In essence, the plea arises if the Amgen parties succeed in persuading the court that the true interpretation of claim 19 (and the claims dependent thereon) is that any difference (no matter how small) in molecular weight by SDS-PAGE is sufficient to constitute a difference for the purpose of claim 19.

121. In the application for the patent as filed [A2/1] and the patent as granted [A2/2], example 10 disclosed the results of carbohydrate composition analyses on recombinant EPO and human urinary EPO isolates. The former was substantially different to the latter.

122. Accordingly the teaching of the application as filed and the patent as granted was that the polypeptide products of the invention were substantially different from naturally occurring EPOs in terms of the carbohydrate composition and hence in their molecular weights.

123. As a result of the TBA decision, Amgen proposed certain amendments to the specification which, in particular, involved the deletion of the passage on page 29 lines 17-26 of the granted patent which contained the description of the carbohydrate composition analyses referred to above. The B2 specification thus has this passage deleted.

124. Accordingly, the patent as applied for and as granted contained only a disclosure to the effect that recombinant EPO had substantially different carbohydrate composition and molecular weight to naturally occurring EPO. Insofar as the matter deleted enables the Amgen parties now to contend that the disclosure in the patent as amended is of recombinant EPO which has only some small difference either in carbohydrate composition or molecular weight then matter in the form of information has been impermissibly added by way of the deletion.

125. Further, it was plain from the application as filed and the patent as granted that the reference to "carbohydrate composition" was to the monosaccharide proportions – see p.65 lines 4-29 of the application. If, as now appears to be suggested (Cummings 2 § 72 [F3/2]), on the proper construction of claim 20 any difference in glycosylation, detected by any method, will amount to a difference in average carbohydrate composition, then the deletion of the passage referring to the carbohydrate composition analyses has resulted in added matter and/or extension of protection.

Claims

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 of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of recticulocytes and red blood cells and to increase hemoglobin 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.

3. A cDNA sequence according to Claim 1 being a ~~or 2.~~

~~4. A~~ monkey species erythropoietin coding DNA sequence ~~according to Claim 3~~.

~~5~~ 4. A DNA sequence according to Claim 4 3 and including the protein coding region set forth in Table V.

~~6~~ 5. A genomic DNA sequence according to Claim 1 or 2.

~~7~~ 6. A human species erythropoietin coding DNA sequence according to Claim 6 5.

~~8~~ 7. A DNA sequence according to Claim ~~7~~ 6 and including the protein coding region set forth in Table VI.

~~9~~ 8. A DNA sequence according to Claim 1 or 2, covalently associated with a detectable label substance.

~~10~~ 9. A DNA sequence according to Claim 9 8, wherein the detectable label is a radiolabel.

~~11~~ 10. A single-strand DNA sequence according to Claim 9 8 or ~~10~~ 9.

~~12~~ 11. A DNA sequence according to Claim 1, coding for [Phe^{15}]hEPO, [Phe^{49}]hEPO, [Phe^{145}]hEPO, [His^{7}]hEPO, [Asn^{3}des-Pro^{2} through Ile^{6}]hEPO, [des-Thr^{163}through Arg^{166}]hEPO, or [Δ27-55]hEPO.

~~13~~ 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.

~~14~~ 13. A transformed or transfected host cell according to Claim ~~13~~ 12 which host cell is

capable of glycosylating said polypeptide.

~~15~~ 14. A transformed or transfected mammalian host cell according to Claim ~~14~~ 13.

~~16~~ 15. A transformed or transfected COS cell according to Claim ~~14~~ 13.

~~17~~ 16. A transformed or transfected CHO cell according to Claim ~~14~~ 13.

~~18~~ 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, 8~~ or ~~12~~ 11.

~~19~~ 18. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to Claim ~~18~~ 17.

~~20.~~ 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 recticulocytes and red blood cells and to increase hemoglobin synthesis or iron uptake and characterized by being the product of ~~procaryotic or~~ eucaryotic expression of an exogenous DNA sequence and which has higher molecular weight by SDS-PAGE from erythropoietin isolated from urinary sources.

~~21. A polypeptide according to Claim 20 characterized by being the product of eucaryotic expression of an exogenous DNA sequence.~~

~~22~~ 20. A glycoprotein polypeptide according to Claim ~~20~~ 19 having an average carbohydrate composition which differs from that of human erythropoietin isolated from urinary sources.

~~23~~ 21. A polypeptide according to Claim 19 or 20, ~~21 or 22,~~ wherein the exogenous DNA sequence is a cDNA sequence.

~~24~~ 22. A polypeptide according to Claim ~~20,21~~ 19 or ~~22~~ 20, wherein the exogenous DNA sequence is a genomic DNA sequence.

~~25~~ 23. A polypeptide according to Claim 19 or 20, ~~21 or 22,~~ wherein the exogenous DNA sequence is carried on an autonomously replicating circular DNA plasmid or viral vector.

~~26~~ 24. A polypeptide according to any one of Claims ~~20~~ 19 to ~~25~~ 23, further characterized by being covalently associated with a detectable label substance.

~~27~~ 25. A polypeptide according to Claim ~~26~~ 24, wherein said detectable label is a radiolabel.

~~28~~ 26. A polypeptide product of the expression in a ~~procaryotic or~~ eucaryotic host cell of a DNA sequence according to any of ~~Claims~~ claims 1, 2, 3, 5, ~~6, 7~~ and ~~8~~ 7.

~~29~~ 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 recticulocytes 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, ~~6-7~~ and ~~8~~ 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.

~~30~~ 28. A process according to Claim ~~29~~ 27, characterized by culturing a host cell of any one of Claims ~~13~~ 12 to ~~17~~ 16.

~~31~~ 29. A process according to Claim ~~29~~ 27 or ~~30~~ 28 for production of a polypeptide of any one of Claims ~~20~~ 19 to ~~25~~ 23 and ~~28~~ 26.

~~32~~ 30. A pharmaceutical composition comprising a polypeptide produced in accordance with the process of Claim ~~29, 30~~ 27, 28 or ~~31~~ 29 and a pharmaceutically acceptable diluent, adjuvant or carrier.

~~33~~ 31. A pharmaceutical composition according to Claim ~~32~~ 30 comprising a polypeptide of any one of Claims ~~20~~ 19 to ~~25~~ 23 and ~~28~~ 26.

~~34. An antibody substance characterized by immunoreactivity with erythropoietin and with a synthetic polypeptide having a primary structural conformation substantially duplicative of a continuous sequence of amino acid residues extant in erythropoietin isolated from urinary sources except for any polypeptide comprising a sequence of amino acid residues entirely comprehended within sequence:~~

~~A P P R L I C D S R V L E R Y L L E A K E A E N I T~~

~~35. An antibody according to Claim 34, which is a monoclonal antibody.~~

~~36. (was 53). An antibody according to Claim 34, which is a polyclonal antibody.~~

~~37. An antibody acoding to Claim 34, which is immunoreactive with erythropoietin and a synthetic polypeptide having the sequence selected from the sequences:~~

~~V P D T K V N F Y A W K R M E V G~~

~~K E A I S P P D A A S A A~~ and

~~V Y S N F L R G K L K L Y T G E A C R T G D R~~