Exhibit A, Part 1

AMGEN v. ROCHE

THE ROCHE PARTIES' SKELETON ARGUMENT ON THE 605 PATENT

INTRODUCTION

1. This action is one of a number that are to be heard together. They all relate to the preparation of recombinant erythropoietin ("EPO").

2. This action concerns EP(UK) 0 148 605 ("the 605 patent") which was applied for on 12th December 1984 claiming priority from four earlier US applications. No issue arises on the question of priority. Although the patent arose out of work done by Amgen Inc., the proprietor is Kirin-Amgen Inc. The patent has been the subject of an exclusive licence to various Johnson & Johnson companies. For the purposes of the trial, nothing turns on these. In this skeleton (and in our skeleton on the 678 patent), we refer to these companies collectively as the Amgen parties.

3. The patent was granted on 25th July 1990 and was then subject to opposition in the European Patent Office by a number of parties, including the Defendant Roche Diagnostics GmbH. We refer in this skeleton (and in our skeleton on the 678 patent) to our clients collectively as the Roche parties.

4. This action was commenced on the day of grant and was originally due for trial together with the Roche parties' action against the Amgen parties for infringement of EP 0 411 678 ("the 678 patent") and certain other patents of the Roche parties which were then in issue. The grant of these patents was also opposed in the European Patent Office. Because of the uncertainty as to which, if any, of the claims of the patents as granted would survive opposition, the parties proposed that the actions should be stayed pending final resolution of the issue of validity at the European Patent Office.

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5. So far as concerns the 605 patent, the claims of the patent as granted did not survive the opposition procedure but a different set of claims was granted, being the claims proposed in the 11th Auxiliary Request. Reference will have to be made to some aspects of the decision of the Technical Board of Appeal ("TBA") of 21st November 1994 (T412/93) [M/1] but for present purposes it is sufficient to recite that:

   (i) Claim 3 as granted was held to be insufficient insofar as it extended to cover a cDNA sequence encoding human EPO. The only relevant enabling disclosure of a cDNA sequence was of one encoding monkey EPO.

   (ii) Claim 20 as granted was anticipated.

6. These findings however were overcome (in the opinion of the TBA) by the amendment to claim 3 to limit the claim to monkey cDNA and by the addition to old claim 20 (now claim 19) of a requirement that the recombinant polypeptide should have a "higher molecular weight by SDS-PAGE from EPO isolated from urinary sources". Much turns in this action on the effect of those two amendments.

7. There was then a dispute as to the form in which the specification as amended should be drafted which resulted in a further decision of the TBA on 26th March 1998 (T636/97) [M/2]. During the course of that hearing, Amgen put forward a number of amendments to the specification in response to the TBA's earlier determination that the specification did not enable human cDNA (see esp. §5.5 of the decision). The patent as amended was published on 13th December 1998.

8. Of particular relevance to this dispute is that, notwithstanding the fact that claim 3 was held to be invalid in so far as it extended to human cDNA sequences, Amgen are suing Roche for the marketing of recombinant EPO produced using a human cDNA sequence and contend that claim 1 is wide enough to cover a cDNA sequence encoding human EPO.

9. The inventor obtained, from a Dr. Goldwasser, supplies of fragments of urinary EPO from which he obtained certain sequence information, which he used to design probes. As is apparent from the description in the patent, the inventor was unable to identify a tissue source from which to obtain mRNA which might have provided a route to human cDNA. Instead he used his probes to isolate and then obtain the sequence for genomic EPO DNA. This sequence forms the Table VI sequence in the patent.

10. The Roche parties do not contend that the work carried out by the inventor in pursuing the genomic route to the genomic sequence was lacking in inventive step.

11. Likewise the inventor carried out work on monkeys. He artificially elevated the amount of EPO in the monkeys by making them anaemic and by this route obtained monkey cDNA from which he obtained the sequence for monkey cDNA EPO.

12. The Roche parties contend that the patent is invalid on the grounds that it relates (in part) to a mere discovery, that it is insufficient and that there is impermissible added matter.

13. We propose to deal with the issues in the following order:

(i) Common general knowledge
(ii) Construction
(iii) Mere discovery
(v) Sufficiency
(vi) Infringement
(vii) Added Matter.

COMMON GENERAL KNOWLEDGE

The addressee of the 605 patent

14. Before the TBA, it was common ground (see §4 of the TBA decision of 21/11/94 [M/1]) that the skilled person should be treated as a team of 3 - a PhD 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. The TBA however accepted that the composition of the team might vary depending on the knowledge and skills required by the different aspects of the 605 patent.

15. The experts in this case broadly accept this (see Wall 1 §45 [F1/5], Brammar 1 §45 [H/1] and Clausen 1 §59 [H/2]). More specifically whereas consideration of the construction and sufficiency of claim 1 would primarily involve input from a molecular biologist, consideration of claim 19 would involve a molecular biologist and a cell biologist with experience of glycoproteins.

The law

16. The common general knowledge is that which is generally known and regarded as a good basis for further action by the bulk of those engaged in the art in question. It is not enough that a piece of information is known to a witness or published in a document, even one which has been widely circulated and read. However, it is not necessary that the information be retained in the mind of the skilled person so long as he knows it exists and would refer to it as a matter of course as a reliable foundation for further work. See *Beloit v. Valmet* [1997] RPC 489 at 494-495 and *Raychem's Patents* [1999] RPC 497 at 503-504.

DNA aspects

17. The Roche parties submit that the following was common general knowledge in 1983/84. (We have not included a considerable amount of basic information which is included in the primer or otherwise appears to be uncontroversial.)

18. *DNA cloning (Brammar 1 §§25-44 & 49-50 [H/1], Brammar 2 §§5-15 [H/6])*

(1) - There was a laboratory manual, the "Maniatis manual" ("Molecular Cloning – A Laboratory Manual" by Maniatis, Fritsch & Sambrook), which had been published in 1982 and which was universally used by molecular biologists interested in cloning DNA. Much of the teaching in it would have formed part of the common general knowledge.

- More specifically, there were two basic strategies that could be used to attempt to isolate the DNA of interest. The first of these involved screening cDNA libraries with a suitable probe and the second involved screening genomic libraries.

(2) cDNA libraries:

- cDNA libraries could be made from tissues in which the mRNA of interest was being expressed. By 1983, the Okayama & Berg technique was widely accepted as a method for constructing cDNA libraries by reverse transcription from the mRNA. But the cDNA approach was only available if a suitable source of mRNA could be found.

(3) Genomic DNA libraries:

- Techniques for making genomic libraries had been published by the Maniatis group in 1978 and their library (the "Lawn library") had been made widely available to other researchers up until the end of 1982.

- The techniques used by the Maniatis group (light partial digestion followed by size fractionation and insertion of the correctly sized fractions into a phage vector) meant that the Lawn library was an excellent library which was highly representative of the genomic DNA. There was a very high probability that the gene of interest would be present in this library.

(4) Mixed oligo probing / protein sequencing:

- The mixed oligo probe technique was well established by 1983 and had resulted in the successful cloning of numerous cDNAs. It was particularly useful in detecting cDNA clones derived from sources which provided extremely low levels of the relevant mRNA. It was described in the Maniatis manual as the method of choice for screening cDNA libraries if protein sequence information was available.

- In order to design mixed oligo probes, protein sequence information was needed. Protein sequencing was a well-established technique, improved in sensitivity by the introduction of the gas-phase sequencer in 1982. N-terminal sequence information could be obtained or, if sufficient protein were available, the protein could be cut into fragments using trypsin or another reagent and the fragments sequenced. Fragments containing tryptophan or tyrosine (which have low-degeneracy codons) could be identified for sequencing by their absorbance at 280nm. Such fragments would be particularly suitable for making mixed oligo probes.

(5) cDNA versus genomic DNA:

- The advantages of cDNA libraries were that they did not contain copies of the introns and that they contained only copies of mRNA from expressed genes. This latter point could also be a disadvantage, in that if the gene of interest was not expressed, there would be no corresponding cDNA in the library.

- There were advantages in using a cDNA rather than a genomic DNA to express the protein of interest in that the cDNA was easier to manipulate and express. The cDNA route was the preferred route to obtaining DNA for use in expression if a source of mRNA was available.

19. *EPO as a target for cloning (Brammar 1 §§45-55 [H/1], Wall 1 §§65-68 & 74-75 [F1/5], Fritsch 2 §§2-3 [H/9])*

- A number of groups considered EPO to be a particularly suitable target for cloning. But there were two problems facing the skilled person wishing to clone EPO.

- The major problem facing a skilled person who wanted to obtain human EPO DNA was the absence of a suitable tissue source of human EPO mRNA from which a cDNA library could be constructed. The Roche parties submit that it was common general knowledge that no suitable tissue source had been identified.

- Secondly, there was a paucity of EPO protein sequence information. This was due to the fact that EPO is present in the body in only minute quantities. The only practical source of significant quantities of uEPO was the urine of Japanese aplastic anaemia patients who had been allowed to remain highly anaemic.

- Miyake (who had access to these patients) and Goldwasser had succeeded in purifying EPO from urine. Dr Goldwasser was known to possess the only supply of significant quantities of purified uEPO. Amgen was able to overcome the problem of protein sequence information by obtaining from Dr Goldwasser sequenceable quantities of uEPO tryptic fragments.

20. *DNA aspects that were not common general knowledge*

As we have noted, a suitable tissue source for human EPO mRNA was not common general knowledge. Nor were the following matters (we expand on these below in the section on insufficiency of claim 1 with respect to human cDNA under the headings "cell expression" and "synthetic DNA"):

- It was not common general knowledge that cDNA could be made via expression of a genomic clone in a host cell. This was not an accepted route.

- The techniques of gene synthesis were not within the skill and knowledge of the skilled person. They were practised only by a few specialist groups.

Glycobiology and protein chemistry aspects

21. The Roche parties contend that the following was common general knowledge in 1983/84 and would have formed the background against which the 605 patent would have been read (again, we have omitted basic material which is in the primer or which otherwise appears to be uncontroversial – see Clausen 1 §§14-58 [H/2] for the matters below and a more detailed exposition):

- Glycoproteins generally consist of a mixture of glycoforms, the oligosaccharide portions of which have different structures and properties. A number of factors can influence the nature and distribution of glycoforms in a preparation of a glycoprotein, including:
  - (if isolated from natural sources) the individuals from which it has been obtained or (if made recombinantly) the species and tissue origin of the cell used; and
  - the treatment of the glycoprotein, including the process by which it is purified and its storage thereafter.

- Natural sources of (glyco)proteins could contain proteases or glycosidases which needed inactivation if degradation of the material of interest was to be avoided, and there were several ways in which that could be achieved.

- There were numerous techniques available for use in purification of the (glyco)protein from the source material. These techniques took advantage of different properties of the (glyco)protein of interest such as size, charge, hydrophobicity and affinity for other species such as antibodies.

- Generally, several different purification steps would be used sequentially. The aim of the protein chemist was to try to achieve a high degree of purification with reasonable yield.

- As different glycoforms have different properties, the glycoforms present in a preparation depend on the purification steps used and the point at which cuts are taken between fractions retained and those rejected.

- (Glyco)protein samples could be analysed by SDS-PAGE. Glycoproteins tend to run as broad bands on SDS-PAGE because of the heterogeneity caused by the presence of a variety of glycoforms. SDS-PAGE is not a precise technique, but a simple way to obtain an approximate assessment of the purity and apparent molecular weight of a sample.

- Glycoprotein samples could also be subjected to carbohydrate composition analysis to determine the identity and quantity of the different monosaccharides present. This technique was not very accurate, and there was an error of around ± 10% for quantification of each monosaccharide.

CONSTRUCTION

The law

22. The scope of any claim of a patent is to be determined in accordance with the provisions of section 125 of the Patents Act 1977. By sub-section (1) an invention is to be taken to be that specified in the claim as interpreted by the description and any drawings contained in the specification and by sub-section (3) the Protocol on the Interpretation of Article 69 applies to sub-section (1). The Protocol is set out on page 922 of Terrell and requires claims to be interpreted as defining a position which combines fair protection for the patentee with a reasonable degree of certainty for third parties.

23. It is plainly important both for considerations of validity and infringement for the true scope of the claim to be ascertained and, in theory, this should be done without regard to specific questions of infringement and validity that may arise on the facts of a given case. Often the question of construction that arises is whether the claim extends to cover a potential infringement which falls outside

the literal wording of the claim. To meet this, the courts in this country (and in other countries that are signatory members of the EPC) have developed a doctrine of equivalence which, in this country, is the doctrine of purposive construction propounded by Lord Diplock in *Catnic Components v. Hill & Smith* [1982] RPC 183 as explained by Hoffman J. in *Improver Corporation v. Remington Consumer Products* [1990] FSR 181.

24. What is less well developed in law is the circumstances in which, having regard to the contents of the specification and the requirements of the Protocol, claims should be given an interpretation narrower than their strict literal meaning. The facts of this case raise such an issue.

25. The objective of Article 69 of the EPC and its Protocol is to secure uniformity of approach to claim construction throughout the member states of the EPC. The combined objective of Section 125 and the Protocol is to require the court to discern from the language of the claim, taken in the context of the wording of the specification, the objective purpose of the inventor (see Jacob J. in *3M v. Plastus Kreativ* [1997] RPC 737 at 747). The question that arises in the present case is the extent to which the doctrine of purposive construction can be invoked so as to limit the scope of a claim so as to ensure that the claim does not:

(a) extend so as to cover that which is not described in the specification and which has expressly been held not to be enabled by the disclosure in the specification; and

(b) confer on the patentee a monopoly which it has expressly disclaimed in order to obtain grant and to overcome oppositions.

26. The question has arisen in a different form in circumstances where it was contended that on its true construction a claim extended so as to cover a particular piece of prior art which was referred to in the body of the specification. In *Beloit v. Valmet* [1995] RPC 705 at 720 Jacob J. stated as follows: