EXHIBIT 1

FEB 15 1999 18:49 FR AIRD & BERLIS 416 863 1515 TO 401664753#180544 P.02/43
FEB-15-1999 17:15

Federal Court of Canada
Trial Division

Section de première instance de
la Cour fédérale du Canada

Date: 19990215

Docket: T-2784-97

BETWEEN:

KIRIN-AMGEN INC. and JANSSEN-ORTHO INC.

Plaintiffs

- and -

**HOFFMANN-LA ROCHE LIMITED/
HOFFMANN-LA ROCHE LIMITÉE (formerly BOEHRINGER
MANNHEIM CANADA LTD./LTÉE)**

Defendant

REASONS FOR JUDGMENT

REED, J.:

[1] The plaintiffs bring a patent infringement action, to which the defendant responds that the particular claim of the patent in issue is not valid, and that the alleged infringement, in any event, has not been proven. The patent, number 1,339,047, (sometimes referred to as the 'Lin Patent') carries the title "Production of Erythropoietin". Human erythropoietin (EPO) is a glycoprotein hormone produced by the kidneys that stimulates the bone marrow to produce red blood cells and the precursors to red blood cells (reticulocytes). It is composed of a

FEB 15 1999 18:49 FR AIRD & BERLIS
FEB-15-1999 17:18 416 863 1515 TO 4016647534180544 P.03/43

protein "backbone" of 165 amino acid links that is folded and joined to itself in certain places by two disulphide bonds. (The diagrams of EPO placed in evidence have the appearance of a folded bicycle chain.) There are several sugar (carbohydrate) branches attached to the amino acid protein backbone, three long and one short. Recombinant human erythropoietin (rhEPO), the subject matter of the patent, is a manufactured glycoprotein similar in structure and function to human erythropoietin. The manufactured glycoprotein is a product of DNA technology.

[2] The plaintiffs claim that the defendant has infringed the '047 Patent by distributing in Canada, a recombinant human EPO called RECORMON and intends to infringe further by selling this product in Canada. It is claim 1 of the patent that is in issue:

> A glycoprotein product having a primary structural conformation of human erythropoietin as set forth in Figs. 5A to 5E, said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and *having a higher molecular weight on SDS-PAGE than human urinary EPO.* [Emphasis added.]

[3] The glycoprotein described in claim 1 has three characteristics: (1) a primary structural conformation of human erythropoietin as set forth in the patent; (2) the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells; (3) a higher molecular weight on SDS-PAGE than human urinary EPO. There is no dispute about the validity of the first two described characteristics. There is no dispute that the defendant's RECORMON product has those characteristics. It is the third characteristic that is the focus of the present action.

[4] The defendant argues that the third element of claim 1 is vague and ambiguous and

FEB 15 1999 18:49 FR AIRD & BERLIS
FEB-15-1999 17:16 IRIL DIVISION 416 863 1515 TO 4016647538180544 P.04/43

therefore the claim is invalid for failing to meet the requirements of subsections 34(1)(e) and 34(2) of the *Patent Act*, R.S.C. 1985, c. P-4. The defendant argues that the disclosure fails to correctly and fully describe the invention as required by paragraph 34(1)(a) of the *Patent Act*, and it fails to set out in full and clear terms the method for making the composition of matter in such a way as to enable any person skilled in the art to make it as required in paragraph 34(1)(b) of the *Patent Act*.[1] (Counsel relied upon paragraph 34(1)(b) in his oral argument although it is not referred to in the Statement of Defence.) The defendant argues that even if the claim is valid, the plaintiffs have not proven that the defendant's product infringes the patent.[2]

---

[1] (1) An applicant shall in the specification of his invention
(a) correctly and fully describe the invention and its operation or use as contemplated by the inventor;
(b) set out clearly the various steps in a process, or the method of constructing, making, compounding or using a machine, manufacture or composition of matter, in such full, clear, concise and exact terms as to enable any person skilled in the art or science to which it appertains, or with which it is most closely connected, to make, construct, compound or use it;

. . .

(e) particularly indicate and distinctly claim the part, improvement or combination that he claims as his invention.

(2) The specification referred to in subsection (1) shall end with a claim or claims stating distinctly and in explicit terms the things or combinations that the applicant regards as new and in which he claims an exclusive property or privilege.

[2] Both counsel argued by reference to R.S.C. 1985, c. P-4 even though paragraph 34(1)(e) was repealed by S.C. 1992, c. 1, s. 113 and all of section 34 was repealed and replaced by S.C. 1993, c. 15, s. 36. The substance
contd ...

FEB 15 1999 18:50 FR AIRD & BERLIS 416 863 1515 TO 4016647534180544 P.05/43
FEB-15-1999 17:17

[5] The patent in issue was originally part of a more comprehensive patent application. That application was filed on December 12, 1984. It also carries the title "Production of Erythropoietin". On August 19, 1994, the application for the '047 patent was divided from this application. The '047 patent issued on May 27, 1997. The rest of the original application, being the subject of conflict proceedings, is still pending in the Canadian Patent Office.

Construction / Validity - Applicable Law

[6] The Court is to construe a patent as would a person skilled in the art to whom the patent is directed. This may require evidence to explain the meaning of words and technical matters, and to apprise the Court of relevant information relating to the particular "art" in question. When construing patent claims, the claims should be read in the light of the specification taken as a whole. They should be read by a mind willing to understand, being both fair to the patentee and the public. In general, notes of the inventor or evidence as to what that person thought had been invented or how the patent should be read, are not relevant.

[7] Patent claims are to be construed as of the date of issue of the patent. This was made clear by the Federal Court of Appeal in *AlliedSignal Inc.* v. *Du Pont Canada Inc. et al.*

... contd

has not changed although the replacement legislation (ss. 27(3) and 27(4)) makes it clear that the specification requirements are to be part of the patent application if that was not clear before.

(1995), 61 C.P.R. (3d) 417.[3] Counsel for the defendant argues that the statement in *AlliedSignal* is *obiter dicta*. He states that on balance the authorities indicate that it is the date of the filing of the original application that should be used in construing a patent.[4] He states that the Court in *AlliedSignal* overlooked the Supreme Court's comments in *Pioneer Hi-Bred Ltd. v. Canada (Commissioner of Patents)*, [1989] 1 S.C.R. 1623, at 1638, that there is a need for an adequate description in a patent to enable someone to put the invention into practice, *as could the inventor at the time of his application.*

[8] Insofar as the date as of which the patent should be construed is concerned, counsel for the plaintiffs argues that the relevant date does not matter in this case and that the patent was both unambiguous and sufficiently detailed to allow a person skilled in the art to follow it

---

[3] The relevant passage from the decision is:

> As a prefatory remark, it ought to be pointed out that a patent is to be construed at the date it is issued. Any doubt about such date is conclusively settled by reference to the French version of a statement made to that effect by Pigeon J. in *Burton Parsons Chemicals Inc. v. Hewlett-Packard (Canada)*, [1976] 1 S.C.R. 555 at p. 560, 17 C.P.R. (2d) 97 at p. 101, 54 D.L.R. (3d) 711 (where the words "la date de la deliverance du brevet" are used).

[4] *Wellcome Foundation Ltd. v. Novapharm Ltd.*, unreported, July 31, 1998, Docket: T-2998-91 at paragraph 69 (F.C.T.D.); *AT&T Technologies Inc. v. Mitel Corp.* (1989), 26 C.P.R. (3d) 238 at 257 - 261 (F.C.T.D.); *Pioneer Hi-Bred Ltd. v. Canada (Commissioner of Patents)*, [1989] 1 S.C.R. 1623 at 1638; *Burton Parsons v. Hewlett-Packard*, [1976] 1 S.C.R. 556 at 560; *Abbott Laboratories Ltd. v. Nu Pharm Inc.* (1998), 78 C.P.R. (3d) 38 at pp. 53-54, Footnote 8 (F.C.T.D.); *Nu-Pharm Inc. v. Abbott Laboratories Ltd.*, unreported, September 28, 1998, Docket: A-84-98 at paragraph 10 (F.C.A.); *Re Institut Pasteur Patent Application* (1995), 76 C.P.R. (3d) 206 at 216 (Patent Appeal Board and Commissioner of Patents); *Faulding Canada Inc. v. Pharmacia SpA*, unreported, June 30, 1998, Docket: T-421-97 at paragraphs 7 to 9 (F.C.T.D.).

at both the date of its application and the date of its issue.

[9] I consider that I am bound by the decision in *AlliedSignal* and should construe the patent as of the date of its issue. I will however also make reference to evidence from the earlier period of time since it may be relevant to the interpretation at the later period of time or, on appeal, a higher Court may consider it important to have the findings before it.

[10] When dealing with patent actions, the Court should first construe the claim alleged to be infringed[5] and then consider its validity[6] or infringement.[7] In this case, because the validity of the patent claim is challenged on the ground of ambiguity and insufficiency, validity is closely linked to construction. It is more closely linked than, for example, in a challenge based on obviousness or anticipation. I will therefore consider the construction and the invalidity arguments together, by reference to the following elements of the claim: molecular weight/apparent molecular weight; SDS-PAGE; human urinary EPO; a "higher" molecular weight. I will then set out some observations on the witnesses and on matters of evidence. Lastly, I will deal with the infringement and the licensing of Janssen-Ortho Inc.

---

5 *Electric and Musical Industries, Ltd. et al. v. Lissen, Ltd. et al.* (1939), 56 R.P.C. 23 (per Lord Russell of Killowen) at p. 39; *Lovell Manufacturing Co. v. Beatty Bros. Ltd.* (1962), 41 C.P.R. 18 (Ex. Ct.) at pp. 70-71.

6 *American Cyanamid Co. v. Bark Pharmaceuticals Ltd.*, [1976] R.P.C. 231 (Ch. D.) at p. 234; *Xerox of Canada Ltd. et al. v. IBM Canada Ltd.* (1977), 33 C.P.R. (2d) 24 (F.C.T.D.) at p. 42.

7 *Dableh v. Ontario Hydro* (1996), 68 C.P.R.(3d) 129 (F.C.A.)at pp. 142-143.

FEB 15 1999 18:50 FR AIRD & BERLIS 416 863 1515 TO 401664753#180544 P.08/43
FEB-15-1999

Molecular Weight / Apparent Molecular Weight

[11] Molecular weight is the mass or weight of one molecule of a substance. It is measured in 'Daltons', abbreviated as 'D' or 'Da'. Molecular weight is the sum of the weights of the component atoms that form the molecule. For example, the atomic weight of hydrogen, the simplest element, is 1, that of carbon is 12, and that of oxygen 16. Thus, the molecular weight of water, being composed of one atom of oxygen and two atoms of hydrogen, is the sum of the atomic weights of an atom of oxygen (16 Da) and two of hydrogen (1 Da each) for a total of 18 Daltons. The sugar glucose is composed of six atoms of carbon, twelve atoms of hydrogen and six atoms of oxygen giving it a molecular weight of 180. This kind of calculated molecular weight, based on the known atomic weights of the various atoms, and the atomic composition of the molecule, is referred to by a number of different terms, i.e., 'theoretical', 'actual', or 'absolute' molecular weight.

[12] Protein molecules are very large. Each protein molecule contains thousands of atoms because each is composed of chains of many smaller molecules linked together. Proteins therefore have molecular weights in the thousands to hundreds of thousands of Daltons. (One thousand Daltons, a kilo-Dalton, is abbreviated as 1kD or 1kDa.) Because of the size of many protein molecules and because their composition is not always precisely known, one cannot calculate their molecular weight with the degree of precision that is possible for simpler molecules. This is particularly true of a glycoprotein such as EPO. One determines instead the molecule's "apparent molecular weight". SDS-PAGE is one process that is used for such determination. (Methods for more exact measurement, such as mass spectroscopy, exist now

FEB 15 1999 18:51 FR AIRD & BERLIS 416 863 1515 TO 401664753#180544 P.09/43
FEB-15-1999

that did not exist at the date of the patent application.)

[13] I turn then to the difference of views concerning the interpretation of the patent insofar as the term "molecular weight" is concerned. It is asserted by Dr. Sytkowski[8] that the patent claim is ambiguous because it refers only to the "molecular weight" of EPO, not the "apparent molecular weight". I prefer the evidence of Dr. Sawyer and Dr. Strickland that any person skilled in the art would read the claim knowing that it meant apparent molecular weight: that is, the characteristic of large glycoprotein molecules that is measured by SDS-PAGE.

SDS-PAGE

[14] As has been mentioned, SDS-PAGE is a process used to determine the apparent molecular weight of proteins. SDS-PAGE is an acronym for sodium dodecyl sulphate and polyacrylamide gel electrophoresis. SDS is a detergent used to coat (saturate) the protein samples to be tested so that they are covered with negative electrical charges. The saturation with SDS renders the proteins' own original positive or negative charges unimportant. The denaturing process also unfolds the protein molecule so that its bundled shape does not affect its movement through an electrical field. SDS does not bind to the carbohydrate branches.[9]

---

[8] Throughout these reasons I will sometimes refer to the evidence of both defence expert witnesses, Dr. Sytkowski and Dr. Hasselbeck, and other times to only one. When I mention only one, it may be that both take this view, but the evidence of one seemed to best capture the point being expressed and therefore only that one is mentioned.

[9] A description of the structure of the erythropoietin molecule is found supra para. 1 (infra para. 29).

FEB 15 1999 18:51 FR AIRD & BERLIS 416 863 1515 TO 401664753#180544 P.10/43
FEB-15-1999 17:18

[15] Electrophoresis is a process in which the protein samples are placed in an electrically charged field and travel through a medium (in this case a polyacrylamide gel) between the two oppositely charged sides of the field (in this case from the top of the apparatus, which is negatively charged, towards the bottom, which is positively charged). The speed with which the proteins move through the gel (their mobility) will be determined by their size. Smaller proteins will move faster than larger proteins. SDS-PAGE is thus used to estimate the size of the protein, which is an analogue to its molecular weight. The molecular weight is determined by the position of the protein in the gel after a period of time of exposure to the electrical field.

[16] Once an SDS-PAGE test has been run, the results must be recorded in a visible form. One method of doing this is to soak the gel in a dye solution or in a chemical mixture containing silver. If dye is used, the dye molecules bind to the proteins and when the gel is washed free of excess dye, the proteins can be seen with the eye because of the binding of the dye. The silver reaction process is a more sensitive test than the dye process. Deposits of silver occur at the location of the protein in the gel.

[17] Another way of making a visual record of the test results is called Western Blot. It is even more sensitive than dye or silver. After SDS-PAGE is run, the proteins on the gel are transferred to a chemically reactive membrane. The proteins bind to this membrane in the same relative positions that they occupied in the original SDS-PAGE gel. Then antibodies that recognize and bind to the protein are applied to the membrane. The location of the binding of

FEB 15 1999 18:51 FR AIRD & BERLIS 416 863 1515 TO 4016647534180544 P.11/43

these antibodies to the protein is recorded.

[18] The size and intensity of the band recorded by Western Blot will depend upon the amount of protein sample tested and upon the conditions and time employed by the investigator in running SDS-PAGE, in a manner similar to the way an image on a photograph varies with the light conditions under which it is taken and the developing process used. Because the Western Blot method is sensitive, the protein bands will appear broader than when recorded by the dye or silver techniques. A band or range of weights occurs because the molecules are not completely identical one to another; there can be variations in the composition of the carbohydrate branches.

[19] While claim 1 of the Patent does not contain a specific reference to the method to be employed to record the test results from SDS-PAGE, the disclosure of the patent at page 64, lines 23-24, and page 65, lines 20-21, refers respectively to "western blot analysis and SDS-PAGE" and "Western blot and SDS-PAGE analysis."[18] A fair reading of the patent then indicates that the method of recording the test results that should be used is Western Blot.

[20] I turn then to Dr. Sytkowski and Dr. Haselbeck's evidence. They assert that SDS-PAGE and Western Blot analysis are not precise enough for the purpose the patent requires them to serve. They state that the molecular weights of human and recombinant EPO fall within the same range (30,000 to 40,000 Da) and are indistinguishable when compared by

---

[18] Example 10 of the Patent.

FEB 15 1999 18:51 FR AIRD & BERLIS
FEB-15-1999 17:46
416 863 1515 TO 4016647534180544 P.12/43

SDS-PAGE. They also assert that the patent lacks sufficient description of the test parameters to allow someone skilled in the art to know what was done by the inventors in testing the characteristics of the patented rhEPO and to allow others skilled in the art to conduct a similar test, to determine whether an rhEPO that they might manufacture infringes the patent.

[21] I am not persuaded that these arguments are well founded. The Patent does not recommend the use of SDS-PAGE for determining a numerical value for the respective molecular weights of uEPO and rhEPO. It requires an assessment of the comparative molecular weights of the two substances. I cannot conclude that the use of SDS-PAGE as a method of determining comparative molecular weights for the substances in question is inappropriate, or leads to vague and incompatible results. I think I need make no further reference to the evidence, in this regard, than to note that the defendant itself uses that test technique, and not merely for comparative purposes but also for the more specific assessments of the numerical values of the molecular weights of its rhEPO.

[22] I turn then to the argument that even if SDS-PAGE is an appropriate test technique to assess the characteristic in question, the claim and disclosure are still not sufficient because they do not contain any information about the test parameters under which the test should be run.

[23] I do not need to refer to the evidence relating to the test parameters in detail. It suffices to note that Dr. Sawyer's evidence was that SDS-PAGE is the most reliable, most

often used, repeatable and consistent method of measuring the relative apparent molecular weights of glycoproteins such as EPO. He gave evidence that it was a test technique routinely taught to undergraduates, that the test parameters identified by Drs. Sytkowski and Haselbeck were ordinary test parameters commonly dealt with by skilled workers conducting SDS-PAGE, and that a skilled worker would know which apparatus and experimental parameters to use for the protein of interest.

[24] Dr. Sawyer's evidence was that the choice of test parameters is so obvious that they are often not included in test results published in scientific literature and that he was not surprised that the Lin Patent did not list the precise conditions under which the SDS-PAGE test should be performed. For example, the "type and percentage of gel that is used", the "duration of the test" and "the amount of electrical charge" would be obvious to a person experienced in running such tests. The need to avoid "overloading" would also be obvious to a skilled worker, i.e., it is desirable to use the smallest amount of the sample being tested that can give a record of the test result.

[25] When Dr. Haselbeck was asked in cross-examination to describe how he would conduct a test, being given only the information in the Patent, he had little difficulty doing so. In addition, any effect a particular change in a test parameter would have on the mobility of the EPOs through the gel would apply equally to both a sample of uEPO and a sample of the rhEPO, if they are run side-by-side on the same test. Drs. Sytkowski and Haselbeck do not satisfactorily explain how any significant variability in result would occur when the same

experimental protocol is applied to compare the relative migrations of side-by-side samples in adjacent lanes of the same gel.

[26] Some of the test parameters to which Dr. Sytkowski and Dr. Haselbeck refer relate to the visual record of the test results, not the SDS-PAGE test itself. Here again, a satisfactory explanation has not been given as to how changes in the parameters would alter the conclusions drawn from the visual record of the test when the changes apply to the recording of the position of both samples. For example, while the intensity of the image may vary with sample size, its position in the gel will not and it is the position of the protein in the gel that is significant. I conclude that SDS-PAGE is an appropriate test technique to assess the comparative molecular weights of recombinant and human urinary EPO.

Human Urinary EPO

[27] As noted, EPO is a protein hormone produced by the kidney, which travels in the bloodstream to the bone marrow and stimulates the bone marrow to produce red blood cells. EPO is produced in such small amounts that it does not seem possible to isolate human EPO (sometimes abbreviated as hEPO) from the blood. However, when individuals have a disease such as aplastic anemia, which is characterized by bone marrow failure, the kidneys overproduce EPO in response to the anemia caused by the inability to make red blood cells, and EPO collects in the urine. This EPO is called human urinary EPO (huEPO). This can be isolated and collected in small amounts.

[28] Research into the structure and characteristics of EPO was originally inhibited because of the inability to isolate and collect sufficient pure samples of human EPO. The first purification of human urinary EPO was carried out by Drs. Miyake, Kung and Goldwasser in the late 1970s. They began with 2,550 litres of urine obtained from persons in Japan who had aplastic anemia. The urine from these patients was collected because in Japan, at the time, patients did not often receive blood transfusions to treat anemia. Blood transfusions increase the oxygen carrying capacity of the blood and concomitantly reduce circulating EPO levels. Drs, Miyake, Kung and Goldwasser subjected the urine to a series of purification steps to yield a few milligrams of purified EPO (uEPO). This was reported in Miyake, Kung & Goldwasser, "Purification of Human Erythropoietin" (1977) 252 *Journal of Biological Chemistry* 5558 (sometimes referred to as the Miyake-Goldwasser process). Shortly before the date of the patent application (December 1984) another method of purification, a two step process, was reported in Yanagawa, Hirade, Sasaki, Chiba, Ueda & Goto, "Isolation of Human Erythropoietin with Monoclonal Antibodies" (1984) 259 *Journal of Biological Chemistry* 2707. Still later another process was developed. It was reported in Krystal, Pankratz, Farber & Smart, "Purification of Human Erythropoietin to Homogeneity by a Rapid Five-Step Procedure" (1986) 67 *Blood* 71.

[29] As noted above, the human EPO molecule has a backbone of 165 amino acid links to which are attached three long and one short sugar (carbohydrate) branches. At the end of the branches are a special type of carbohydrate, sialic acid, which prevents the molecule being metabolized by the liver. If the end carbohydrates are removed the resulting product is asialo

human urinary EPO. If one removes not merely the sialic acid ends but the whole carbohydrate branch the protein backbone of the molecule is left. In addition, two different fractions (II and IIIA) of EPO were identified by Miyake, Kung and Goldwasser as having been collected in their purification process. These were later designated the α and β forms.

[30] The defendants argue that the patent claim is vague because: (i) uEPO was not and is not readily available so that the comparative testing to rhEPO, as required to determine whether infringement of the patent exists, cannot be easily done; (ii) there is no description of the type of uEPO that is to be compared to an allegedly infringing rhEPO; (iii) there is no standard uEPO and neither the degree of purity, the purification process, nor the potency of the uEPO to be used is specified.

(i) availability

[31] The literature is replete with references to the initial difficulty of obtaining enough uEPO for research purposes. Once the recombinant product became available, however, it was used, and a greater amount of investigation could be undertaken; there was less need for uEPO. In any event, difficulty in obtaining a substance necessary to do the comparative testing required by a patent does not itself render a patent invalid. The difficulty is a condition that will exist for all persons doing research in the field. In addition, a very small amount of uEPO is needed for any one SDS-PAGE test. Most importantly, however, uEPO was and is available. The Miyake-Goldwasser paper sets out a procedure for purifying uEPO that someone wishing to produce uEPO can follow. Also, uEPO could be and can be purchased

FEB 15 1999 18:53 FR AIRD & BERLIS 416 863 1515 TO 401664753#180544 P.17/43
FEB-15-1999 17:19

commercially.

[32] Dr. Sytkowski followed the Miyake-Goldwasser procedure to produce uEPO in 1980. The results of the 1980 effort were unsatisfactory because the urine storage procedure that he directed be used led to degradation of the protein. Also, he had difficulty acquiring urine containing the required concentration of EPO. There was, however, no inadequacy in the description of the purification procedure set out in the Miyake-Goldwasser paper. Dr. Sytkowski used a different purification process in 1987 to produce uEPO. In 1995-96, Dr. Strickland produced uEPO by following the procedure described in the Miyake-Goldwasser paper. He used urine that had been obtained from aplastic anemia patients in China. This uEPO was used in the tests conducted in August 1998 in New Jersey, for the purposes of the present litigation (the New Jersey experiments).

[33] Human urinary EPO was commercially available by 1983-1984 from the Toyobo Co. Ltd. of Japan. In a paper published in 1985, Dr. Sytkowski refers to sources used by him for the research results reported in Sytkowski & Fisher, "Isolation and Characterization of an Anti-Peptide Monoclonal Antibody to Human Erythropoietin" (1985) 260 *Journal of Biological Chemistry* 14727:

> Highly purified human urinary erythropoietin (70,400 u/mg), provided by the Division of Blood Diseases and Resources, NHLBI, NIH, was used in the initial phases of this study. For more detailed experiments, purified erythropoietin was obtained from Toyobo. [Footnotes omitted.]

In another paper, received for publication the following year, the authors (of whom Dr. Sytkowski is one) wrote ". . . we used human urinary erythropoietin (80,000 units/mg)

FEB 15 1999 18:53 FR AIRD & BERLIS 416 863 1515 TO 4016647534180544 P.18/43
FEB-15-1999 17:46

purified by immunoaffinity chromatography and supplied by Toyobo" (Choi, Wojchowski, & Sytkowski, "Erythropoietin Rapidly Alters Phosphorylation of pp43 an Erythroid Membrane Protein" (1987) 262 *Journal of Biological Chemistry* 2933). There is reference in Sasaki, Yanagawa, & Chiba, "Isolation of Human Erythropoietin with Monoclonal Antibodies" (1987) 147 *Methods in Enzymology* 328, at 331, to uEPO being available in 1987 from Toyobo Co. Ltd. of Japan.

[34] In 1997, uEPO was commercially available from at least three sources: ICN Pharmaceuticals Inc., Aurora, Ohio (using the Yanagawa et al. process); StemCell Technologies Inc. of Vancouver (using the Krystal et al. process); Sigma-Aldrich Chemie GmbH, Deisenhofen, Germany. [1] Thus, uEPO was available to someone needing it for the purposes of comparing it to recombinant EPO both at the date of issue of the patent and the date of application.

(ii) type of uEPO

[35] Claim 1 of the patent refers to "human urinary EPO" as the substance to which the rhEPO should be compared. Dr. Haselbeck states that this is an insufficient description because each person's uEPO is different, depending upon the glycosylation of the molecules, and because there are several different types of uEPO (asialo and fully native).

[36] Dr. Sawyer's evidence was that a person reading the patent would know that it was pooled source human urinary EPO that should be used. (It was the only source available at

FEB 15 1999 18:53 FR AIRD & BERLIS 416 863 1515 TO 4016647534180544 P.19/43

the time the patent was drafted.) He states that a person reading the patent would assume you would not use the asialo EPO for any sort of SDS-PAGE comparison. He adds that if there is any doubt as to the meaning of the term in claim 1, the Lin Patent, on page 64, line 27 states that the "human urinary EPO" used in the SDS-PAGE test was "pooled source human urinary extract" which means EPO extracted from the urine pooled from several patients.

[37] The relevant passage of the disclosure, at pages 64-65, is set out below. I will italicize the phrases that are particularly relevant:

> A preliminary attempt was made to characterize recombinant glycoprotein products from conditioned medium of COS-1 and CHO cell expression of the human EPO gene in comparison to *human urinary EPO isolates* using both Western blot analysis and SDS-PAGE. These studies indicated that the CHO-produced EPO material had a somewhat higher molecular weight than the COS-1 expression product which, in turn, was slightly larger than the *pooled source human urinary extract*. All products were somewhat heterogeneous. Neuraminidase enzyme treatment to remove sialic acid resulted in COS-1 and CHO recombinant products of approximately equal molecular weight which were both nonetheless larger than the resulting *asialo human urinary extract*. Endoglycosidase F enzyme (EC 3.2.1) treatment of the recombinant CHO product and *the urinary extract product* (to totally remove carbohydrate from both) resulted in substantially homogeneous products having essentially identical molecular weight characteristics.

[38] Dr. Haselbeck interprets the passage from the disclosure set out above as saying that several ". . . human urinary isolates" were tested, and that the conclusion was reached that all such products were ". . . somewhat heterogeneous", and that only the "pooled source human urinary extract" provided the SDS-PAGE results wherein the recombinant EPO was "slightly larger." He argues that this indicates that various urinary samples were tested individually and differed from each other with respect to molecular weight on SDS-PAGE. He argues that it is not apparent from either the claim or the disclosure what type of human urinary EPO is meant in the specification.

[39] Dr. Sawyer states that the term "human urinary EPO isolates" in line 23 on page 64 is the "pooled source urinary extract" in lines 27 and 28 of page 64 (he further reads this portion of the Lin Patent as saying that the recombinant EPO had a higher apparent molecular weight than pooled source urinary EPO on SDS-PAGE). He notes that the scientific literature regularly referred to "human urinary EPO" as EPO extracted from the urine of a number of patients, specifically those suffering from aplastic anemia. Two articles co-authored by Dr. Sytkowski, one in 1983, and one in 1987, are among the writings that describe the starting point for the purification of uEPO as being "pooled urine samples obtained from patients with aplastic anemia" (Sue & Sytkowski, "Site-specific Antibodies to Human Erythropoietin Directed Toward the NH_2-terminal Region" (1983) 80 *Prod. Natl. Acad. Sci.U.S.A.* 3651, and Wojchowski, Sue, & Sytkowski, "Site-specific Antibodies to Human Erythropoietin: Immunoaffinity Purification of Urinary and Recombinant Hormone" (1987) 913 *Biochimica et Biophysica Acta* 170).

[40] In my view a person skilled in the art would interpret the patent as Dr. Sawyer has done. Also, I am not persuaded that the use of the words "a preliminary attempt" in the passage quoted above undercuts that interpretation. Nor does the fact that there are admitted erroneous results reported in the first and second full paragraphs on page 65. The inventors erroneously thought they could characterize rhEPO as different from uEPO by reference to the composition of the carbohydrate branches. It is admitted that the results reported are erroneous. This does not affect the validity of the preceding paragraphs that describe the difference in molecular weights observed on SDS-PAGE.

(iii) purity, purification process, potency

[41] While an international standard for rhEPO has been articulated, this is not the case for uEPO. Also, it is accepted, as noted above, that the molecular weight (i.e., apparent molecular weight) will not be a discrete number but will be a range and appear as a band on SDS-PAGE, or as a Gaussian or Poisson curve when depicted in graph form.

[42] With respect to the argument that a less pure preparation of uEPO would differ in molecular weight from a more pure sample, Dr. Sawyer's evidence, which I accept, was that he knew of no evidence, nor scientific rationale for believing that a crude uEPO preparation would run with a higher or lower apparent molecular weight on SDS-PAGE with Western blot than would purified material. [2]

[43] Dr. Haselbeck's evidence was that the manner in which uEPO was purified and fractionated would affect its molecular weight, since during the purification process certain parts of the molecule can be removed to a greater extent than others. Dr. Haselbeck referred to the Yanagawa purification process as support for his opinion that purification procedures affect molecular weight. He stated that that process required the denaturing of EPO with SDS and binding it to a monoclonal antibody column. He stated that this leads to the inactivation of EPO.

[44] Dr. Sawyer, whose evidence I prefer, disagreed with this assertion, stating that the SDS should only straighten out the EPO molecule and should not cleave off any carbohydrate branches that might affect the activity of the molecule or its mobility on SDS-PAGE. He states that he has

FEB 15 1999 18:54 FR AIRD & BERLIS 416 863 1515 TO 401664753#180544 P.22/43
FEB-15-1999 17:21

never observed a purification method that uses antibodies that preferentially isolate one molecular weight population over another, and that Dr. Haselbeck has not referred to any real life examples, that he is merely speculating. Also, in the New Jersey experiments, both uEPO prepared by Dr. Strickland following the Miyake-Goldwasser procedure and uEPO purchased from ICN, which had been purified using the Yanagawa method, were run in the SDS-PAGE test and they did not exhibit different molecular weights.

[45] Reference was also made by Dr. Sytkowski to the fractions II and IIIA (subsequently named α and β) identified in the Miyake-Goldwasser paper. It was stated that these are likely to have different molecular weights because they were subsequently found to have different carbohydrate contents. At the same time, the Miyake-Goldwasser paper describes the two fractions as having the same mobility on SDS-PAGE. Also, the patent, at page 10, states that "the α and β forms differ slightly in carbohydrate components, but have the same potency, biological activity and molecular weight". Dr. Sawyer's evidence was that while fractions II and IIIA (i.e., forms α and β) might have different carbohydrate contents, there would be no recognizable difference between the two on SDS-PAGE, and that both fractions would appear to have the same apparent molecular weight.

[46] I turn then to the assertion that a failure to specify the potency of the uEPO makes it difficult to determine what uEPO to use. I do not think it is necessary to describe what is meant by potency. It is sufficient to note that in the evidence it is sometimes referred to as specific activity or *in vivo* activity.

[47] Dr. Sawyer's evidence, which I accept, was that while *in vivo* biological activity might in certain circumstances be related to molecular weight, he reads and he believes others would read the patent as requiring a purified uEPO having a specific activity in the range reported in the Miyake-Goldwasser paper as having been obtained from the purification procedure there described, that is around 70,000 - 80,000 units/mg. He notes that the ICN specification sheet shows that the product used in the New Jersey experiments was around 80,000 units/mg and that a specific activity of 81,600 is reported in Yanagawa, "Isolation of Human Erythropoietin with Monoclonal Antibodies" (1984) 259 *Journal of Biological Chemistry* 2707. Roche (then Boehringer Mannheim) purchased several samples of uEPO from Sigma-Aldrich in 1995-1996, which Dr. Haselbeck used for experiments. He did no tests to determine the purity or *in vivo* activity. Roche also purchased uEPO from StemCell in 1995-1996. No tests were done to determine its purity. The *in vivo* activity was tested and found to be 68,000 units/mg (a 1993 sample was found to be about 78,000 units/mg). A skilled reader would know that a sample having an *in vivo* activity below 70,000 - 80,000 would not be appropriate for use.

Higher Molecular Weight

[48] One would not expect the word "higher" to be the subject of dispute. The characteristic described by the word higher would seem to be fairly obvious. That a small difference is meant by that description is clear from the phrases in the disclosure "somewhat higher molecular weight than the COS-1 expression product" and "slightly larger than the pooled source". The defendant argues, however, that a comparative description is not precise, that one should first identify the numerical range within which uEPO and rhEPO fall and then

assess whether the allegedly infringing rhEPO falls within the uEPO numerical range. In addition, given that one is dealing with weight ranges, the defendant argues that one cannot say that a given rhEPO is heavier than uEPO if the ranges overlap and are offset. It is argued that the two have to be entirely separate. Dr. Haselbeck's opinion was that:

> the way to approach this is to look if the proteins you analyze are within a certain range you have defined before, and when you compare them, . . . if you want to say they have a higher molecular weight, it would mean they have to be completely separated from each other . . . [Transcript pages 654 - 5.]

[49] I am not persuaded that this is correct. When one reviews the literature a variety of numerical ranges are found, depending upon the laboratory conditions and the state of the art at the time.

[50] Dr. Haselbeck's own review of the literature, seeking a numerical range for the molecular weight of uEPO, seems arbitrary. He leaves out Dr. Sytkowski's assessment, in 1980, that the molecular weight was 25,000 - 30,000 Da. He rejects Dr. Goldwasser's correction, in 1983, of his 1977 estimate (about which more will be said later) despite Dr. Sawyer's explanation that the earlier estimate was likely incorrect because tube gels may have been used.

[51] Dr. Haselbeck referred to a paper written in 1997 by Drs. Kung and Goldwasser ("A Probable Conformational Difference Between Recombinant and Urinary Erythropoietins" (1977) 28 *PROTEINS: Structure, Function, and Genetics* 94), for the statement that the molecular weight of the β form of uEPO derived through the Miyake-Goldwasser purification process as assessed by gel electrophoresis according to Laemmli had now been determined to

be 37,000 instead of 34,000 and this therefore shows the lack of consistency in the molecular weight of uEPO. Dr. Haselbeck relies on this paper even though the data reported also shows rhEPO as having a higher molecular weight than uEPO.

[52] Some of the literature refers to uEPO and rhEPO migrating identically. A small difference may for some purposes be important, for others insignificant, depending upon the purpose for which, and the perspective from which, an author is writing. It is necessary to consider statements that are made in journal articles, the authors of which are not witnesses before the Court, with care. Also, some rhEPO may have the same molecular weight as the uEPO referred to in the patent. If this is the case, that rhEPO will not infringe the patent.

[53] Most importantly, however, no numerical values are given in the patent for the apparent molecular weight of the human urinary EPO or the inventor's recombinant EPO. No numerical value is imposed on the difference that the characteristic set out in the claim describes. The patent simply asks the skilled reader whether the apparent molecular weight of the rhEPO is higher than the apparent molecular weight of uEPO as measured on SDS-PAGE.

[54] I find Dr. Sawyer's evidence convincing:

> a skilled reader of the Lin Patent could give a reasonable interpretation of words ". . . having a higher molecular weight on SDS-PAGE than human urinary EPO" as used in the Lin Patent and could compare the relative migrations of the two EPOs by running them side-by-side on the gel and would have sufficient information to know whether a sample of recombinant EPO had a higher molecular weight than uEPO on SDS-PAGE. [Para. 52 (page 26) of Exhibit P-67.]

The Witnesses

[55] The credibility of the expert witnesses in this case is a very important factor. Four expert witnesses were called: Dr. Sytkowski and Dr. Haselbeck for the defendant, Dr. Sawyer and Dr. Strickland for the plaintiffs.

[56] Dr. Sytkowski was not credible. His extreme partisanship and lack of veracity was demonstrated in his statements that he could not see at the New Jersey experiment because his view was blocked, and that he was kept from the room during the running of the experiment. Not only does this not make sense, since if it had occurred he surely would have made protestations at an earlier date, it is directly contradicted by the evidence of Dr. Sawyer, whom I believe. Dr. Sawyer stated that Dr. Sytkowski himself suggested that they all leave the room until the gel run was completed because there was nothing to see. Dr. Johnson, who actually ran the experiment, testified that, if Dr. Sytkowski had really been standing eight to ten feet away, as he said he was, he would have been in Dr. Johnson's office rather than his laboratory.

[57] Dr. Sytkowski's less than ethical approach can also be seen in the way he conducted himself in 1981, when he took pictures of slides of Dr. Goldwasser's results, without his permission, during a presentation by Dr. Goldwasser of those results at an annual meeting of the American Society of Haematology, and subsequently published those results as his own, without attribution to Dr. Goldwasser. It is reasonable to assume that this had some relationship to the difficulty he had obtaining purified uEPO from Dr. Goldwasser during the

early 1980s. His assertion to the Court that uEPO was not available from Dr. Goldwasser takes on a different connotation in that context.

[58] Dr. Haselbeck's characterization of the relevant literature repeatedly shows that his enthusiasm to support his employer's position leads him to overstate or misstate the conclusions found therein. I do not propose to review all his evidence but will illustrate the problem that exists with his evidence by reference to two examples.

[59] As support for his assertion that the upper range of the molecular weight of uEPO is around 39,000 daltons, he cited the 1977 Miyake-Goldwasser paper. In 1983, Dr. Goldwasser corrected this statement:

> It has previously been reported to have a molecular weight of 39,000. We have reexamined the molecular weight and found it to be closer to 34,000.

[60] Dr. Haselbeck, however, when reviewing the literature states that the 39,000 figure was *confirmed* by Weiss, Kavinsky, & Goldwasser, "Characterization of a Monoclonal Antibody to Human Erythropoietin" (1982) 79 *Prod. Natl. Acad. Sci.* 5465, by Dordal & Goldwasser, "Function and Composition of the Carbohydrate Position of Human Urinary Erythropoietin" (1982) 10(11) *Experimental Haematology* 133, and by Sue & Sytkowski, "Site-specific Antibodies to Human Erythropoietin Directed Toward the NH_2-terminal Region" (1983) 80 *Prod. Natl. Acad. Sci. U.S.A.* 3651. When a statement is made that results have been confirmed a reader expects that independent testing has been done that led to the same result. The literature in question, to which Dr. Haselbeck refers for his assertion that the

39,000 figure was confirmed, is not of that nature. It merely contains references to the Miyake-Goldwasser paper.

[61] When Dr. Haselbeck was asked for his explanation of Dr. Goldwasser's statement in 1983 that they now believed the molecular weight number to be closer to 34,000 daltons, Dr. Haselbeck asserted that "closer" meant anything less that 39,000 and this could be 38,000 - indeed, he initially said it could be 38,999. Such evidence lacks credibility and demonstrates Dr. Haselbeck's lack of objectivity.

[62] It will be obvious from the repeated reliance on Dr. Sawyer's evidence that is found in these reasons, that I found his evidence to be credible and reliable. At one point, his credibility seemed to be questioned by counsel because he admitted that he was not familiar with all the text of some articles of which he was listed as an author. I find his explanation credible, that in academic works of joint authorship this is not an unusual situation, and that the persons whose names come first in a list of joint authors are likely to have had more responsibility for the article than those whose names are buried in the middle.

[63] Dr. Strickland was careless on at least two occasions. After he purified the uEPO, when conducting assay tests, his micro pipettes were incorrectly calibrated and the numbers he recorded were inaccurate. He subsequently discovered this and in May of 1996 re-assayed the relevant fractions with new pipettes. When he provided information to counsel in 1998, for the purposes of this litigation, he provided the earlier inaccurate numbers, rather than the

corrected versions. Subsequently, when he provided the corrected numbers he forgot to recalculate all the numbers in the relevant table by reference thereto. The errors, however, do not cast doubt on the veracity of the corrected results. Nor does the fact that not all the fractions could be re-assayed because those of lesser concentration had been thrown away. The calculation errors have no effect on the purified uEPO itself; they do not change the properties of that product.

Some Matters of Evidence

[64] Comments follow on three issues that arose in the evidence: (i) decisions in other jurisdictions; (ii) proceedings in the patent office; (iii) claims of confidentiality.

(i) Decisions in Other Jurisdictions

[65] Counsel placed decisions in two other proceedings before me. One by the Federal Court of Australia, *Genetics Institute, Inc. v. Kirin-Amgen, Inc. (No. 3)* (No. VG868 of 1995, June 25, 1998), the other by the Technical Board of Appeal of the European Patent Office (*Opposition by Genzyme Corporation and five others to Kirin-Amgen Inc.'s Patent No. 0148605*, Case Number T 0412/93 - 3.3.4., November 24, 1994).

[66] The Australian decision, not a final decision, found the claim of the corresponding Australian patent to be invalid. The European Patent Office Board of Appeal, in a final decision, found the claim to be valid.

[67] The Australian Court found that the terms "somewhat higher molecular weight" and "slightly larger size" were vague and uncertain criteria and that the claim had "no practical utility since such a test [SDS-PAGE] would rely on an analytical procedure which is known to have a degree of imprecision and require direct comparison to human urinary erythropoietin, a substance that is particularly difficult to obtain".

[68] The European Patent Office decision on the other hand found that the "higher molecular weight" . . . 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 rEPO exhibits a higher molecular weight than a given uEPO made available to the public." It is trite law that neither has any binding or precedential value in this Court.

(ii) Patent Office Proceedings (File Wrappers)

[69] In general, the proceedings that occur is the Patent Office, in the course of pursuing a patent application, are not relevant to patent construction. Counsel for the respondent sought to introduce evidence of those proceedings in this case and I reserved judgment thereon, stating that a decision would be made after I had heard argument as to the relevance of the material. The argument was never pursued and the claim to rely on the patent office proceedings was abandoned. The material relating thereto is thus not considered to be part of the evidence.

(iii) Confidentiality of Other Tests

[70] Dr. Strickland was asked, in cross-examination, whether he had purified any other batches of uEPO besides that used in the New Jersey experiment. He responded that he was not at liberty to answer that question because the information was confidential. The confidentiality that was asserted (on the instructions of U.S. counsel) was litigation privilege (a privilege that protects material prepared in anticipation of litigation). The batches in question were apparently prepared for litigation in the United States and in the United Kingdom. I expressed doubt as to whether, once Dr. Strickland was called as a witness, he could properly claim privilege with respect to other batches of uEPO he had prepared. I requested that there be argument on the point before I would make a ruling. Counsel for the defendant indicated that he would not pursue the matter but was content to have the record show that the witness had refused to answer. Nevertheless, in argument, counsel for the plaintiff presented argument as to why the claim should fall within litigation privilege. He submitted that litigation privilege attaches to information produced for foreign litigation, just as it does for information produced for litigation in Canada. He further submitted that there has been neither an implicit, nor an implied waiver of that privilege by Amgen, Inc., the holder of the privilege. The defendant argued to the contrary, stating that by putting Dr. Strickland on the stand, the plaintiff had implicitly waived privilege, particularly since Dr. Strickland's purpose was to testify about the purification of human uEPO. The defendant asserted that Dr. Strickland cannot claim privilege for information on the very issue his testimony was designed to explain.

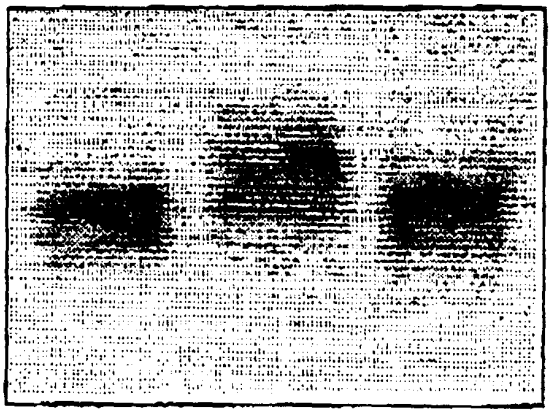
[71] I doubt that a witness in the position of Dr. Strickland can refuse to answer a question so closely related to the evidence he has been called to give, on the basis of a claim for privilege. I do not need, however, to decide this point since in the light of counsel for the defendants' position, and the Court's decision not to insist on an answer by Dr. Strickland, no consequences follow.

Infringement

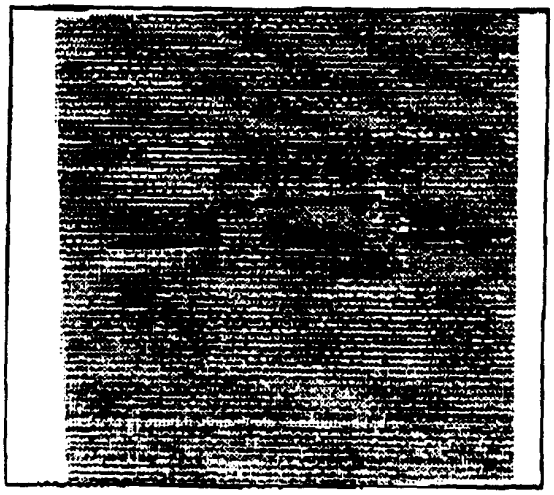
[72] The plaintiffs' infringement claim rests on what has been referred to as the New Jersey experiment. This was conducted on August 13 and 14, 1998, at the R.W. Johnson Pharmaceutical Research Institute (which is affiliated with Janssen-Ortho Inc.) in Raritas, New Jersey, U.S.A. The experiment was supervised by Dr. Sawyer. Representatives of both the plaintiffs and defendant attended. Among those attending for the defendant was Dr. Sytkowski.

[73] Two uEPO samples, one, as noted above, purchased from ICN that had been purified in accordance with the Yanagawa method, and another that had been prepared by Dr. Strickland in accordance with the Miyake-Goldwasser method, were run on an SDS-PAGE test apparatus together with three rhEPOs. The three rhEPOs were NeoRECORMON, Roche's German product, RECORMON, the product Roche intends to market in Canada, and EPREX, the product sold by Janssen-Ortho Inc. in Canada. Two SDS-PAGE gels were run simultaneously in the SDS-PAGE apparatus in case one of the gels was damaged during the experiment.

[74] Photographs of the Western blot paper images of the two SDS-PAGE gels from that experiment show all the rhEPOs as having higher apparent molecular weights than the uEPOs. The samples in the 3rd, 4th and 5th lanes of the gel are respectively, Dr. Strickland's uEPO, RECORMON, and the ICN EPO. The photograph below shows the SDS-PAGE results of those three lanes. RECORMON rhEPO, the centre band, is offset and slightly higher than the bands relating to both urinary EPOs:



[75] A line drawn through the centre of each band results in the following picture:



[76] Consonant with their position that one should first establish a numerical molecular weight range for uEPO and then see if the relevant rhEPO falls within it, Drs. Sytkowski and Haselbeck argue that the difference shown on the SDS-PAGE is simply an experimental difference within the ordinary variations that exist among the various samples of uEPO that are available. Yet Roche has purchased within the past 12 months uEPO from ICN and conducted tests with it. No results from these were placed in evidence by Roche. I recognize that it is for the plaintiff to prove infringement, not for the defendant to disprove it, but I think a negative inference can be drawn from the failure to produce test results that support the defendant's assertion.

[77] Dr. Haselbeck conducted some tests in 1996 that demonstrate the variations in batches of rhEPO made in Germany by the defendant, and some tests using uEPO purchased from StemCell and Sigma-Aldrich that show one batch of the rhEPO as having a lower molecular weight than some uEPO. I do not accept these test results as reason to doubt the findings of the August 1998 New Jersey experiments. Dr. Haselbeck's experiments do not deal with the product that is to be sold in Canada, which allegedly infringes the patent. At most the experiments show that an rhEPO can be made that does not infringe the patent.

[78] Dr. Sytkowski criticizes the August 13-14, 1998 experiment for the following reasons: the manufacturer's instructions were not followed - too thick a gel was used; the test was run for too long a time; the samples were incorrectly loaded; the samples were of different concentrations; salt concentrations were different; the amounts loaded in each lane were less

than the detection limit of the antibodies used for the recording of the test result thereon recommended by the manufacturer.

[79] A 16 percent acrylamide concentration was used in the experiments. The manufacturer's chart indicates that a 10% gel is recommended for resolutions in the 30,000 - 40,000 molecular weight-range. Dr. Sawyer's evidence was that a person skilled in the art would know that for a glycoprotein such as EPO a higher percentage gel would be preferred over the standard shown on the manufacturer's chart. A higher percentage gel would lead to a more accurate determination of molecular weight because the protein moves more slowly in a more concentrated gel. Dr. Sytkowski himself, in a paper published in 1991, reports using a 15% gel. Dr. Goldwasser's 1997 paper reports results using a 15% gel.

[80] The apparatus was allowed to run for five hours, until the molecules were approximately in the centre of the apparatus. The manufacturer's catalogue states that the run time, using a higher voltage than that used in the New Jersey experiment would be 90 minutes, depending on the percentage gel used. Dr. Sawyer's evidence was that if you ran the 16% gel for 90 minutes the proteins would hardly have moved at all. Dr. Sytkowski criticized the run time because "the effect ... is a substantial increase of temperature in the gel due to the electric current". Dr. Sytkowski did not touch the gel at the end of the experiment, nor did he ask to do so. Dr. Johnson who conducted the experiment and handled the gel gave evidence that the electrophoresis plates and the aqueous buffer solution were at room temperature at the completion of the experiment.

[81] Dr. Sytkowski believed the samples were improperly loaded. Dr. Sytkowski said he had no reason to doubt that Dr. Johnson put 20 micro litres in each lane, just that he did not see it (even though he was standing close by). That the loading was reasonable is demonstrated by the fact that the results show each lane to be of similar intensity.

[82] Dr. Sytkowski states that the samples were not prepared uniformly, that, for instance, in sample 1, 2 µl of rhEPO (EPREX) was mixed with 1998 µl of salt containing buffer and of this mixture, 10 µl was loaded in the gel. Sample 6, however, the Strickland urinary EPO, was prepared by mixing 1 µl of it with 39µl of salt containing buffer, and loading 2 µl of the mixture in the gel. In cross-examination, however, Dr. Sytkowski agreed that the different treatment was necessary because the samples were not uniform to begin with. The different treatment rendered the samples, to the extent possible, into the same concentration.

[83] With respect to the criticism that there might have been different amounts of salt mixed with the different samples, Dr. Sytkowski did not perform a calculation to see what the salt concentration was in the different lanes, nor did he provide any evidence as to how different salt concentrations could have had any effect on the movement of the samples through the gel.

[84] Dr. Sytkowski also objected to the test results because the antibody used to detect the protein is described by R & D Systems, Inc., the company from whom it was obtained, as having a "detection limit for rhEPO of approximately 50 ng/lane under both non-reducing and

reducing conditions." The amounts loaded in each lane was less than 50ng. He also notes that there are narrow bands appearing in each lane near the top of the gels and these indicate to him that there were some problems with the sample preparation or the test itself.

[85] These complaints were answered by Dr. Sawyer who noted that when using SDS-PAGE one always tries to load the smallest amount possible in each lane in order to prevent overloading, and that the manufacturer simply has a better product than it is advertising; the results show that the antibody worked. He also notes that there is a contradiction in the R & D Systems Inc. brochure because, for a comparable technique to Western Blot (the Elisa technique), the brochure states that the detection limit is one nanogram. In his view a detection limit of 50 ng in one case and 1 ng in the other does not make sense.

[86] With respect to the narrow bands appearing at the top of the gel, Dr. Sawyer states that he has no idea what these are, and speculates that they might be skin proteins, keratin, caused by somebody inadvertently touching the pipette tip. In any event, they were irrelevant to the test results and did not demonstrate contamination of the samples.

[87] I conclude that none of the criticisms articulated by Dr. Sytkowski undercuts the validity of the August 1998 test results.

Licensing of Janssen-Ortho Inc.

[88] The defendant at the date of the trial was not yet on the market with its RECORMON

FEB 15 1999 18:58 FR AIRD & BERLIS 416 863 1515 TO 4016647534180544 P.38/43
FEB-15-1999 17:25

product. The plaintiffs seek an injunction to prevent the defendant from marketing RECORMON in Canada. That remedy does not require proof that Janssen-Ortho Inc. is a person claiming under the patentee. The entitlement of either plaintiff to the remedy is sufficient to warrant such an order. The plaintiffs, however, are concerned that marketing is imminent and that the present litigation could proceed in such a way that their claim for damages would become relevant. For such a remedy the status of Janssen-Ortho Inc. is relevant.

[89] Kirin-Amgen is the owner of the '047 patent. That patent issued on May 27, 1997, and as noted, was divided from a more comprehensive patent application that had been filed on December 12, 1984. On September 30, 1985, Kirin-Amgen licensed Ortho Pharmaceutical Corporation (now known as Ortho-McNeil Pharmaceutical Inc.) and its affiliates to use and sell in a number of countries, including Canada, products made in the United States of America that are within the scope of the broader patent application. A written agreement to that effect exists. The recombinant EPO used in the EPREX product that is sold in Canada is made in Puerto Rico, a commonwealth of the United States.

[90] In 1986 Ortho Pharmaceutical Corporation gave Janssen-Ortho's predecessor a mandate to market and sell EPREX in Canada. No written licence documenting that agreement can be found. No written notice to Kirin-Amgen of that sub-licence has been found. Nevertheless, it appears that Kirin-Amgen has had notice that Janssen-Ortho's predecessor and now Janssen-Ortho had been sub-licensed to use and sell the EPREX product

in Canada. The EPREX product was launched on the Canadian market in 1990. Since that time, Janssen-Ortho has been paying royalties, first to what was then the Ortho Pharmaceutical Corporation, and more recently to Ortho Biotech Inc. The royalties are then paid to Kirin-Amgen.

[91] The rights acquired from Kirin-Amgen in 1985 were subsequently assigned by Ortho Pharmaceutical Corporation (renamed Ortho-McNeil Pharmaceutical Inc.) to Ortho Biotech Inc. under an Asset Transfer Agreement effective January 1, 1998. Kirin-Amgen consented to this assignment.

[92] Since no written document could be found of the 1986 agreement between Ortho Pharmaceutical Corporation and Janssen-Ortho's predecessor, a written licence agreement was signed by Ortho Biotech, Ortho McNeil, and Janssen-Ortho on November 20, 1998 confirming that Janssen has been sub-licensed since 1986 by Ortho-McNeil's predecessor Ortho Pharmaceuticals to use and sell products containing erythropoietin in Canada. In the agreement, Ortho Biotech also grants to Janssen-Ortho a non-exclusive right to use and sell licensed products containing erythropoietin as provided in the product licence agreement signed between Kirin-Amgen and Ortho Pharmaceuticals on September 30, 1985. Written notice of this agreement was given to Kirin-Amgen (Exhibit D-6).

[93] It is also necessary to note that the Ortho companies are all affiliated. Johnson & Johnson a New Brunswick, New Jersey corporation owns 100% of the voting stock of

FEB 15 1999 18:59 FR AIRD & BERLIS 416 863 1515 TO 401664753#180544 P.40/43
FEB-15-1999 17:23

Janssen-Ortho. It also owns either directly or indirectly 100% of the voting stock of Ortho-McNeil Pharmaceutical Inc. and Ortho Biotech Inc.

[94] Counsel for the plaintiffs argues that applying the test articulated in *Apotex Inc. v. Wellcome Foundation Ltd.* (1998), 79 C.P.R. (3d) 193 (F.C.T.D.) at 300 - 301, (which test is: can the right asserted by the claimant be traced back to the patentee), leads to the conclusion that Janssen-Ortho is a person "claiming under" the patentee for the purpose of section 55 of the *Patent Act*. I agree.

Conclusion

[95] For the reasons given, I find the patent claim in issue to be valid. The defendant's RECORMON product infringes the plaintiffs' patent, since it has a higher molecular weight on SDS-PAGE than human urinary EPO. Thus, an injunction will issue restraining the defendant from marketing, selling or using that product. An order will also issue allowing the plaintiffs damages or accounting of profits should those remedies become relevant. (The defendant as of the date of the trial was not commercially marketing RECORMON.) A decision on costs is reserved, as requested, until counsel have had an opportunity to make submissions thereon.

B. Reed
Judge

OTTAWA, ONTARIO
February 15, 1999

Confidential
AM 67 027218