UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. F. HOFFMANN-LA ROCHE LTD ROCHE DIAGNOSTICS GmbH and HOFFMANN-LA ROCHE INC., Defendants.	CIVIL ACTION NO.: 05-CV-12237WGY

ROCHE'S OPPOSITION TO AMGEN'S MOTION IN LIMINE NO. 8: EXCLUDE ROCHE FROM RELYING ON COMPARISONS BETWEEN ROCHE'S PEG-EPO PRODUCT AND AMGEN'S ARANESP® PRODUCT

I. INTRODUCTION

Evidence concerning the chemical structure and biological function of Amgen's ARANESP® product is highly probative to demonstrate that all chemical compounds that react with the EPO receptor and cause erythropoiesis are NOT covered by the Lin patents' claims. Amgen's infringement case rests on the fallacious proposition that Roche's MIRCERA® product stimulates erythropoiesis by interacting with the EPO receptor and, therefore, must infringe the Lin patents' claims. Amgen would like the jury to believe that every substance that binds and activates the human EPO receptor must be human erythropoietin or something insubstantially different from it. To that end, Amgen witnesses will cite to the Lin patent specification wherein statements were made in an effort to broaden the scope of Lin's alleged invention by describing "other EPO products" such as polypeptide analogs and fragments. Amgen's ARANESP® product is an example of a compound that stimulates erythropoiesis by interacting with the EPO receptor, and as Amgen admits is NOT covered literally or the equivalent of any asserted claim. The jury must hear testimony regarding the nature of ARANESP® in order to fully appreciate that compounds may still stimulate erythropoiesis by interacting with the EPO receptor and NOT infringe the asserted claims.

Moreover, understanding the chemical nature of ARANESP® will provide the jury with a yardstick to determine how chemical compounds are materially changed. Amgen argues that making a product like MIRCERA® is trivial. Indeed, Amgen's difficulties developing an erythropoietic agent with a longer *in vivo* half-life than EPOGEN® is relevant to that issue. Finally, the information about ARANESP® will aid the jury in evaluating what constitutes an unwarranted application of the patent claims under the reverse doctrine of equivalents.

II. FACTUAL BACKGROUND

To defend against Amgen's infringement claims, Roche plans to present evidence concerning the properties of Amgen's erythropoiesis stimulating agent (ESA) ARANESP® that are not covered by any of the claims in suit. Roche will also present evidence that its own ESA, MIRCERA®, falls further outside the claims in suit and, therefore, does not infringe.

ARANESP® is an ESA sold by Amgen that differs from EPOGEN®, in that the ARANESP® molecule contains additional glycosyl functional groups similar to those found in EPOGEN®. These glycosyl groups are added while the molecule is in the cell, much as the EPO of the Lin patents is glycosylated in the cell in which it is manufactured. Amgen faced considerable difficulties in developing a second generation ESA that is designed to have a longer half-life (thus requiring less frequent dosing). The result of Amgen's efforts, ARANESP®, came only after extensive experimentation involving hundreds of compounds. Moreover, Amgen's ARANESP® is patented over the prior art Lin patents and, therefore, must be a non-obvious product over whatever Dr. Lin described.

Roche's accused product, MIRCERA®, is a more radical departure from the product claimed in the Lin patents in that MIRCERA® is produced by isolating a protein outside a cell and then subjecting it to a chemical reaction which covalently binds an artificial functional group (PEG) to produce a new chemical compound having a non-protein, an altered amino acid residue in its polypeptide sequence. The PTO has recognized the distinction of MIRCERA® over other patented ESAs by granting Roche U.S. Patent No. 6,583,272.

Amgen's ARANESP® drug stimulates the EPO receptor, as does erythropoietin claimed by the Lin patents, but works in a different way from the product of the Lin claims. For example, ARANESP® has a half-life (the time it takes for half the drug dosage to clear from the body) three times that of EPO. Roche's MIRCERA® product is even more of a departure from EPO, having a half-life 33 times that of EPO.

Amgen marks the ARANESP® product label with the asserted '698 patent but, in responding to interrogatories, did not identify a single asserted claim as covering ARANESP®, pointing only to unasserted claim 1 of the '698 patent. (Plaintiffs' Supplemental Response to Roche's First Set of Interrogatories (1-12), Feb. 10, 2007 ("Supp. Int. Resp."), at 26). Roche will also present evidence, buttressed by statements by Amgen personnel such as Steven Elliott, that ARANESP® is a different molecule from that described in the Lin patents. Amgen has stated, in prosecuting its European patent application for ARANESP®, that ARANESP® was inventively distinct over the Lin patents and that the Lin patents did not contemplate Amgen's ARANESP® product. (Reply to Communication dated Oct. 30, 1995). Furthermore, in prosecuting the patent that matured into U.S. Pat. No. 7,217,689 (the patent on ARANESP®), Amgen argued that given the state of the art regarding the structure and function of EPO, the claims were inventively distinct over references including Lin. (Response to Office Action, July 11, 2003).

III. ARGUMENT

The Federal Rules of Evidence state that "[a]ll relevant evidence is admissible"; relevant evidence being defined as evidence "having any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence." Fed. R. Evid. 402, 401. *See Fitzgerald*

v. Expressway Sewer Const., Inc., 177 F.3d 71, 75 (D. Mass. 1999) ("Under federal evidentiary standards, the relevancy hurdle is low. . . ."). The evidence Roche will submit regarding ARANESP® is plainly relevant.

A. Statements by Amgen Concerning ARANESP® Are Relevant Admissions That Are Probative of the Application of the Claims to Products

Amgen employees have stated, both in deposition and in statements to the PTO, that ARANESP® is patentably distinct from the EPO of the Lin patents. (Response to Office Action, July 11, 2003). Furthermore, Amgen has implicitly agreed with Roche that none of the asserted claims in suit covers its ARANESP® product. Roche will present these admissions by Amgen to the jury as evidence of what compounds and processes, in Amgen's view, would infringe the asserted claims.

Amgen's admissions about ARANESP® will provide insight into how the asserted claims are or are not applicable to accused products. Such admissions may be significant in an infringement analysis. *See Hampshire Paper Co. v. Highland Supply Corp.*, Civ. 02-32-JD, 2002 WL 1676285, *5 (D.N.H. July 18, 2002) (finding that statement by patentee's counsel that if defendant's products were the same as certain prior art products, there would be no infringement were binding on patentee).

B. The Jury Should Hear Evidence Demonstrating What Constitutes an Equivalent to the Claimed Inventions

Roche will offer proof at trial that it does not infringe under the doctrine of equivalents. Roche's case will include evidence that Amgen agrees with Roche that all ESAs do not, literally or by the doctrine of equivalents, fall within the scope of the asserted claims. (Supp. Int. Resp.; Response to Office Action, July 11, 2003 (statement by Amgen that ARANESP® is an inventive step over prior art Lin patents)). This will

inform the jury as to the limits of equivalents of the Lin claims in suit. Roche will also prove that MIRCERA® is an even further departure from the claims of the Lin patents. If ARANESP®, which is structurally and functionally closer to erythropoietin than MIRCERA®, does not infringe Amgen's patents, then MIRCERA® certainly does not infringe the patents.

Roche will present evidence from the prosecution of Amgen's ARANESP® patent reflecting Amgen's position that ARANESP® is patentably distinct over the Lin patents. (Reply to Communication dated Oct. 30, 1995; Response to Office Action, July 11, 2003). Roche will also show that Amgen developed ARANESP® only after exhaustive experimentation. This evidence will shed light on what features of ARANESP® are distinct over the Lin patents and are not deemed equivalent.

Furthermore, the jury should hear evidence that Amgen's ARANESP® differs substantially in the way it functions in the body from the erythropoietin claimed in the Lin patents. Given that ARANESP® does not satisfy the asserted claims, this evidence gives the jury a useful guidepost as to the range of equivalents to be afforded the Lin patents-in-suit. This evidence is, therefore, relevant and should be permitted.

C. The Jury Should Be Permitted to Hear Evidence Concerning What Constitutes a Material Change to the Product of a Patented Process

Because MIRCERA® is manufactured in Europe and will be imported into the United States, Roche will rebut Amgen's assertion of its process claims[1] by offering evidence that MIRCERA® is materially changed from the product of the patented process claims. 35 U.S.C. § 271(g). What constitutes a "material change" in the product is a

[1] These claims are claims 1 and 2 of U.S. Patent No. 5,441,868, claims 6-9 of U.S. Patent No. 5,618,698, and claim 7 of U.S. Patent No. 5,756,349.

question of fact to be decided by the jury. *Biotec Biologische Naturverpackungen GmbH v. Biocorp, Inc.*, 249 F.3d 1341, 1352 (Fed. Cir. 2001).

Thus, Roche should be allowed to provide evidence that will help the jury to understand what constitutes a material change. To this end, Roche will prove that ARANESP® is substantially different from the inventions of the patents-in-suit both in structure and function. For example, Roche can show that ARANESP® has substantially different biological properties in the body than EPO. "In the chemical context, a 'material' change in a compound is most naturally viewed as a significant change in the compound's structure and properties." *Eli Lilly & Co. v. Am. Cyanamid Co.*, 82 F.3d 1568, 1573 (Fed. Cir. 1995). Given that Amgen has taken the position that ARANESP® does not satisfy the asserted claims of the Lin patents and given that MIRCERA® constitutes an even more substantial change over the EPO of the Lin patent claims, information about ARANESP® shows that MIRCERA® is the product of material changes before being imported.

Furthermore, evidence of the extensive efforts required of Amgen in developing a long half-life ESA drug rebuts Amgen's position that it was a simple matter at that time to pegylate a protein and produce a long half-life drug. Such evidence about ARANESP® supports an inference that the pegylation approach used by Roche was not routine and that Roche's process in producing MIRCERA® constitutes a material change.

D. Evidence That ARANESP® Does Not Infringe the Lin Patent, Is Relevant to Roche's Argument That MIRCERA® Does Not Infringe Under the Reverse Doctrine of Equivalents

At trial, Roche will defend against Amgen's infringement claims by asserting the reverse doctrine of equivalents. Roche will offer proof that, even if MIRCERA® were found to literally infringe Amgen's claims, MIRCERA® is so different in principle from

the invention of the asserted claims that a judgment of infringement would constitute an unwarranted application of the claims beyond the fair scope of the invention.

Evidence that Amgen has obtained patent protection on its ARANESP® product, like the fact that Roche patented MIRCERA® may be *prima facie* evidence of noninfringement under the reverse doctrine of equivalents. *See Amgen, Inc. v. Hoechst Maron Roussel, Inc.*, 339 F. Supp. 2d 202, 300 (D. Mass. 2004) ("attainment of a patent may aid in making a *prima facie* case in support of the reverse doctrine of equivalents"); *Jewish Hosp. of St. Louis v. IDEXX Labs.*, 973 F. Supp. 24, 28 (D. Me. 1997). Evidence of how the Lin patent claims relate to ARANESP® is thus highly relevant to the application of the reverse doctrine of equivalents to MIRCERA®.

E. Roche Does Not Seek to Compare MIRCERA® to Amgen's Embodiment of the Lin Patents

The cases cited here by Amgen in support of its motion are inapposite. In each case, the claimed error was in comparing the accused product to a device said to embody the claims -- rather than to the claims -- to determine if there was direct infringement. *See, e.g., Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1423-24 (Fed. Cir. 1994) (district court erred in using accused product as proxy for claims in direct infringement analysis); *Catalina Lighting, Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1286 (Fed. Cir. 2002) (error in using figures as proxy for claims). These cases support a conclusion that Amgen should be precluded from comparing Roche's product to "Dr. Lin's recombinant EPO" rather than the words of the claim. Here, by contrast, ARANESP® is not a commercial embodiment of the Lin patents. Roche expects to offer evidence concerning ARANESP® because of Amgen's own positions that ARANESP® is not covered by the Lin claims. This evidence, in turn, is relevant as evidence of how the

claims in suit may not be rightfully applied to Roche's MIRCERA® product which lies even further outside the patented claims.

IV. CONCLUSION

For the foregoing reasons, evidence comparing MIRCERA® with Amgen's ARANESP® product is relevant to more than one issue in the case and should not be precluded. Amgen's motion should be denied.

Dated: September 2, 2007
Boston, Massachusetts

Respectfully submitted,

F. HOFFMANN-LA ROCHE LTD,
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CERTIFICATE OF SERVICE

I hereby certify that this document filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and will be delivered to Amgen's trial counsel by electronic mail in the manner requested in the August 29, 2007, letter of Renee DuBord Brown to Thomas F. Fleming. Paper copies will be sent to those indicated as non registered participants on September 4, 2007.

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