Amgen Inc. v. F. Hoffmann-LaRoche LTD et al Doc. 619

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

Exhibits C, D, E, F to the Declaration of Peter Fratangelo, Esq. in Support of Roche's Motion for Summary Judgment that Claim 1 of U.S. Patent No. 5, 955, 422 Is Invalid For Indefiniteness and Lack Of Written Description

Amgen has assented to these documents being filed publicly and will not be filing a motion with the Court seeking to have the documents deemed confidential. Thus, pursuant to paragraph 14 of the Protective Order, Roche is filing these documents in the public record. Roche's previously filed Notice of Service of Confidential Documents In Support of its Motion for Summary Judgment that Claim 1 of U.S. Patent No. 5, 955, 422 Is Invalid For Indefiniteness and Lack Of Written Description (Docket No. 618) is therefore moot.

Dated: July 3, 2007

/s/ Nicole A. Rizzo
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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 paper copies will be sent to those indicated as non registered participants on the above date.

/s/ Nicole A. Rizzo
Nicole A. Rizzo

Dockets.Justia.com

EXHIBIT C

UNITED STATES DISTRICT COURT

DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. F. HOFFMANN-LA ROCHE LTD., a Swiss Company, ROCHE DIAGNOSTICS GmbH, a German Company and HOFFMANN-LA ROCHE INC., a New Jersey Corporation, Defendants.	Civil Action No.: 05-12237 WGY

REBUTTAL EXPERT REPORT OF AJIT VARKI, MD

SUBJECT TO PROTECTIVE ORDER
CONTAINS BOTH ROCHE AND AMGEN CONFIDENTIAL MATERIAL
CONTAINS ROCHE BLA MATERIAL

58. I further understand that as a legal matter, Roche asserts that the process and source limitations of Dr. Lin's product claims are not properly considered for determining whether the claimed products are novel, or whether they were previously found in the prior art. I am informed that Roche's legal analysis is incorrect. In any event, Dr. Bertozzi argues at length that "[l]imiting the claimed product to a human erythropoietin product from a recombinant source does not distinguish the claimed product from human EPO described and existing in the prior art.[27] Contrary to Dr. Bertozzi's arguments, it is my opinion that these process and source

[27] Bertozzi Report ¶ 71.

limitations confer specific structures to the claimed products and that those specific structures are different from the structure of the EPO that was purified from human urine before Dr. Lin made his inventions.

84. Thus, it is not surprising that no recombinant EPO can accurately reproduce the precise structure the mixture of glycoforms in naturally-occurring prior art EPO. When a

gene for a secreted glycoprotein is removed from its normal cellular environment, and inserted into a different type of cell — often from a different species — which is grown under far different conditions than its *in situ* environment in the body, it is completely unsurprising that the glycoprotein that is produced has different glycan structures than the naturally-occurring glycoprotein. One would have understood that it would have been extremely unlikely and practically impossible to reproduce the glycosylation found on naturally occurring EPO because of both the difficulty in reproducing the cell type that normally makes EPO and the difficulty in reproducing the environment in which those cells normally grow.

REDACTED

G. PLASMA OR SERUM EPO HAVE NON-RECOMBINANT GLYCOSYLATION PATTERNS

211. I understand that Roche's experts have opined that prior administration of plasma or serum from one animal to another or from one human to another anticipates or renders obvious Amgen's product claims. I further understand that Roche's expert Dr. Spinowitz has recently supplemented his report on this point. Thus, I reserve my right to supplement my opinion on this topic after I have had an opportunity to carefully review Dr. Spinowitz's arguments. I can comment, however, on Roche's argument at a high level. As I have explained, the glycosylation structures imparted by cells grown in culture are inherently different than those imparted by the cells in the kidney that naturally produce EPO. Therefore, the same logic that leads to my opinion that urinary EPO is different from recombinant EPO applies with equal force

to plasma preparations that may or may not contain EPO.

REDACTED

REDACTED

Executed this 11th day of May, 2007 at San Diego, California.

AJIT VARKI, MD

EXHIBIT D

UNITED STATES DISTRICT COURT

DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. F. HOFFMANN-LA ROCHE LTD., a Swiss Company, ROCHE DIAGNOSTICS GmbH, a German Company and HOFFMANN-LA ROCHE INC., a New Jersey Corporation, Defendants.	)	Civil Action No.: 05-12237 WGY

EXPERT REPORT OF DON H. CATLIN, M.D.

SUBJECT TO PROTECTIVE ORDER

CONTAINS AMGEN CONFIDENTIAL MATERIAL

26. Every protein molecule has a characteristic pI. pI is a reflection of all the charged groups[11] attached to the protein molecule. These charged groups can include certain amino acids.[12] These charged groups can also include post-translational modifications that carry a charge, such as some sugar groups like sialic acid. Often, particular proteins like erythropoietin are made up of a mixture of molecules which differ in their composition of these charged groups. Individual members of such a molecular mixture are known as isoforms. Such proteins and their isoforms can be distinguished by differences in their pI.

REDACTED

[11] Certain chemicals, known as "ions" can gain or lose atoms or electrons in such a way to attain either a positive or negative electrical charge. A protein molecule can have numerous different charged groups, some of which may be negative, and others positive.

[12] Of the twenty amino acids which make up proteins, aspartic acid and glutamic acid are acidic.

REDACTED

58. The details of the methods used to generate the data herein are fully described in the peer-reviewed literature. The IEF method for EPO was first described by Lasne in a letter to Nature in 2000.[20] My colleagues and I have published peer-reviewed scientific articles concerned with the detection of darbepoetin alfa and recombinant human EPO in human urine,[21]

REDACTED

[20] Lasne,F., de Ceaurriz, J., "Recombinant erythropoietin in urine," *Nature* 405: 635 (2000).

[21] Catlin, D.H., Breidbach, A., Elliott, S., Glaspy, J., "Comparison of the isoelectric focusing patterns of darbepoetin alfa, recombinant human erythropoietin, and endogenous erythropoietin from human urine. *Clin. Chem* 48:2057-2059 (2002); Breidbach, A., Catlin, D.H., Green, G.A., Tregub, I., Truong, H., Gorzek, J., "Detection of rHuEPO I urine by isoelectric focusing," *Clin. Chem.* 49:901-907 (2003).

and an extensive review of the history, practice, and detection of doping with EPOs.[22] Exhibits H and I describe the methods we used in further detail.

59. The samples of EPO pharmaceutical products obtained from India, China, Mexico, Argentina, and Korea, as well as the samples of Epogen® and the uEPO standard were prepared for spotting according to the protocol described in Exhibit H.

[22] Catlin, D.H., Hatton, C.K., Lasne, F., "Abuse of Recombinant Erythropoietins by Athletes," In: Molineux G, Foote MA, Elliott S, eds. Erythropoietins and erythropoiesis: Molecular, Cellular, Preclinical, and Clinical Biology. Birkhäuser Verlag, 2003:205-227.

REDACTED

69. Based on these data, my learning, and experience, I make the following conclusions:

(i) The EPO isoforms observed in purified urinary EPO standard obtained from the NIBSC are almost indistinguishable from the EPO isoforms observed in the whole urine of a normal individual.

(ii) All recombinant EPOs tested could clearly be distinguished from both EPO in normal urine and the international standard for urinary EPO. The difference in each case is the presence of several isoforms in urinary EPO which are lacking for each recombinant EPO.

(iii) Amgen's unpurified recombinant EPO contains all of the same glycoform bands as Epogen®, except that it has a lower proportion of the most acidic isoforms and it appears to have 3 additional basic isoforms. Unpurified recombinant EPO could also readily be distinguished from both EPO in normal urine and the international standard for purified urinary EPO.

Executed this 11th day of May, 2007 at Los Angeles, California.

DON H. CATLIN M.D.

EXHIBIT E

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. F. HOFFMANN-LA ROCHE LTD., a Swiss Company, ROCHE DIAGNOSTICS GmbH, a German Company and HOFFMANN-LA ROCHE INC., a New Jersey Corporation, Defendants.	Civil Action No.: 05-12237 WGY

SUPPLEMENTAL EXPERT REPORT OF AJIT VARKI, MD

Contains Amgen/Roche Confidential Material and Roche Restricted Access Confidential BLA/IND Information Subject to Protective Order

REDACTED

27. Dr. Imperiali's statement that it has not been shown that "***all*** recombinant EPO has glycosylation which differs from ***all*** naturally occurring EPO"[46] sets an unrealistically high and practically impossible standard. It is not possible to test all hypothetically possible recombinant EPOs. However, all of the comparison experiments that have been performed on real recombinant EPOs that have actually been produced support my opinion that such differences do exist. Neither Dr. Bertozzi nor Dr. Imperiali has identified any data on any rEPO that contradicts my conclusions.

REDACTED

[46] Imperiali Report ¶ 102 (emphasis added).

REDACTED

Executed this 1st day of June, 2007 at La Jolla, California.

AJIT VARKI, MD

REDACTED

EXHIBIT F

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

Amgen, INC.,	)	
Plaintiff,	)	
vs.	)	No. 05-12237
F. HOFFMAN-LA ROCHE LTD., a	)	WGY
Swiss Company, ROCHE DIAGNOSTICS	)	
GmbH, a German Company, and	)	
HOFFMAN-LA ROCHE INC., a	)	
New Jersey Corporation,	)	
Defendants.	)	

The CONFIDENTIAL videotaped Deposition of EUGENE GOLDWASSER, called by the Defendants for examination, taken pursuant to notice, agreement and under the Rules of Civil Procedure for the United States District Courts pertaining to the taking of Depositions, taken before Richard H. Dagdigian, CSR No.084-000035, a notary public within and for the County of Cook, State of Illinois, and a Certified Shorthand reporter of said State, at the offices of Kaye Scholer LLP, Chicago, Illinois, on the 31st day May 2007,

between urinary EPO and recombinant EPO, and based upon some differences, you suggested that that could be a reason for the differences in potency, is that correct?

MR. MADRID: Objection. That misstates the article.

A The significant word there is "could be". We didn't establish it firmly.

BY MR. SUH:

Q Why could you not establish it firmly?

A Because we don't know the conformation of urinary erythropoietin at all, and at the time this paper was published, something was known of the folded up structure of the recombinant.

Q So in 1987, did anyone know what the -- I'm sorry?

A 97.

Q In 1997, did anyone know what the folded up structure of urinary EPO was?

MR. MADRID: Objection, outside the scope.

A I didn't know. I don't know whether anyone else knew. I knew the literature.

BY MR. SUH:

Q Do people know now?

A No, not to my knowledge.

Q And why is that?

A Nobody has determined a three-dimensional structure of urinary EPO. And it's probably because nobody has ever crystalized it.

Q Why hasn't anyone tried to determine the three-dimensional structure of urinary EPO?

MR. MADRID: Objection, calls for speculation. Outside the scope.

A I -- I don't know why someone didn't do something. That's impossible for me to know.

I can know why we didn't.

BY MR. SUH:

Q Can you tell me why you didn't?

A We never had any success in crystallizing it. I tried and tried and tried.

Q In -- do you know what the term "microheterogeneity" is?

A Yes.

Q In any particular sample of urinary EPO, do you expect that to be a heterogeneous sample or a homogeneous sample?

MR. MADRID: Objection, outside the scope, leading.

respect to what's stated here.

So this is vague and ambiguous, it lacks foundation and it's unfair.

A The way you state that, I think, is incorrect. The evidence may have been complete as far as it went in 1989.

The way you put it is as though someone was not taking into account any of the evidence, all of the evidence that was there.

With all of the evidence that was there, that may be a reasonable statement. But our knowledge has changed since then.

BY MR. SUH:

Q Do you think someone in 1983 or 1984 would have known whether a urinary EPO and recombinant EPO were the same product or not?

MR. MADRID: Objection, vague and ambiguous.

A I'm unclear what you mean by the same product.

BY MR. SUH:

Q Okay. Let me see if I can clarify that.

Do you think they would have known of any differences in secondary structure?

A In secondary structure?

Q Uh hum.
A I don't think anyone would have known it.
Q How about today?
A Today, yes. Well, no. We know a good deal about the secondary structure recombinant EPO. We don't know anything about the secondary structure -- what we know is very scant about the secondary structure of urinary EPO.
Q So even today, one would not know for sure what the differences are between the secondary structure of recombinant EPO and urinary EPO?
MR. MADRID: Objection, vague and ambiguous, misstates the testimony.
A It's -- it's logical, if you don't know something, you can't compare it with something you do know.
BY MR. SUH:
Q Okay. Okay, Doctor, you can put this document aside for now.
A Let's say we break for lunch.
MR. SUH: Oh, sure, that's fine. This is a good time.
A Yes, it's lunchtime.
THE VIDEOGRAPHER: Going off the record at