Exhibit H

Declaration of Howard S. Suh in Support of Roche's Motion for Summary Judgment that the Asserted Claims of the '933 Patent are Invalid for Indefiniteness and Lack of Written Description

UNITED STATES DISTRICT COURT

DISTRICT OF MASSACHUSETTS

AMGEN INC.,	)	
	)	
Plaintiff,	)	
	)	Civil Action No.: 05-12237 WGY
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.	)	
	)	

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

SUBJECT TO PROTECTIVE ORDER

CONTAINS AMGEN CONFIDENTIAL MATERIAL

Health Organization.

III. TESTING FOR EPO DOPING USING ISOELECTRIC FOCUSING

22. In 1998, there arose great concern that cyclists competing in the Tour de France were doping with recombinant human erythropoietin ("rHuEPO"). The discovery of rHuEPO and other drugs in the trunk of automobile just before the race led to a widespread investigation that eventually resulted in recovery of many drug products, confessions from several athletes, and evidence of widespread involvement of cycling teams and coaches.[4] In response to these revelations, the World Anti-Doping Agency was formed. Thus, in 1998, there was great impetus to develop a technique that could accurately and reliably detect the presence of recombinant EPO in the human body separate and apart from the presence of any naturally occurring EPO.

A. THE DOPING CONTROL TEST PROCEDURE

23. The first successful attempt to develop a direct test for rHuEPO in urine came in 1995 with the description of a method for detecting rHuEPO in urine by isoelectiric focusing gel electrophoresis.[5] Although this test had practical limitations, it demonstrated conclusively that the isoform[6] pattern and content of native human EPO present in urine and that of rHuEPO

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[4] Swift EM, "Drug pedaling," *Sports Illustrated* 7-5: 60-65 (1999); Anonymous, "A sport in shame," *Sports Illustrated* 7-27: 28-33 (1998); Jarvis CA (1999) "Tour de Farce," *Br. J. Sport Med.* 33: 142-143

[5] Wide, L., Bengtsson, C., Berglund, B., Ekblom, B., "Detection in blood and urine of recombinant erythropoietin administered to healthy men," *Med Sci Sports Exerc* 27: 1569-1576 (1995).

[6] "Isoforms" are different versions of the same protein which differ in some measurable characteristic. In this report, "isoforms" are versions of EPO which differ in their isoelectric focusing point. "Glycoforms" are versions of the same protein which differ specifically in the structure of their attached sugar structures.

particular sample.

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.

27. The entire analysis consists of four steps: sample preparation; isoelectric focusing, *immuno-blotting*, and visualization. The following description is intended to be a summary for the non-specialist.

1. Sample preparation

28. The task is to prepare the urine sample so that it is suitable for IEF analysis. This involves two steps. The first involves inactivating enzymes that could destroy the erythropoietic proteins before the sample gets to the IEF phase of the analysis. The second is to remove materials in the urine that are detrimental to the analysis. This step involves concentrating the proteins (rHuEPO is a protein). First, we add protease inhibitors (chemicals) to the urine to deactivate enzymes which might otherwise destroy the erythropoietic proteins thereby foiling the analysis. Next, we use specialized filters that remove molecules with low

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[10] A "base" is a substance that can accept protons from acids.

[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.

67/343 70.1015."[18] The package insert for this sample is attached as Exhibit J. This material was originally concentrated from the urine of patients suffering from hookworm anemia in 1968.[19]

56. On February 10, 2007, we also obtained urine samples from normal healthy males and from a male treated with Epogen®. This is material that we generated in a study in which we administered Epogen® to normal human volunteer subjects, for use as a positive control in our EPO doping test to make sure that we could detect recombinant human EPO.

V. METHODS

57. We tested the samples described here using the same procedure we have developed to test athletes' urine samples for EPO doping. We used the same care to process the samples and document the results as we do when we test to determine whether athletes are cheating.

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]

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[18] http://www.who.int/biologicals/reference_preparations/catalogue_de/en/print.html.

[19] Annable, L., Cotes, P.M., and Mussett, M.V., "The second international reference preparation of erythropoietin, human, urinary, for bioassay," *Bull. Wld. Hlth. Org.* 47:99-112 (1972).

[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.

60. The urine samples were prepared for IEF by a series of steps that included centrifugation, filtration, and concentration. The urine samples were included to assess whether both urine samples and pharmaceuticals can be simultaneously analyzed, and whether pharmaceuticals can be detected in urine samples.

61. Approximately 12 mIU of each sample was spotted on the gel and isoelectric focusing gel electrophoresis was performed. Exhibit L shows the image obtained from the gel. Each sample was spotted in one lane. There are 13 lanes numbered consecutively 1-13 from the left. The sample of Normal (known negative) Human Urine (NHU) was spotted in lanes 1 (leftmost lane) and 12 (rightmost lane). The sample of the uEPO International Standard is in lane 13. The sample of Epogen® is spotted in lane 2. The sample of urine collected from a male treated with Epogen® is in lane 3. The sample of cell culture medium (CCM) collected from recombinant EPO-producing cells is in lane 11. The samples of the EPO pharmaceutical products obtained from India, China, Mexico, Argentina, and Korea are in lanes 4-10. The Figure is labeled with the identity of each sample.

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[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.

65. As expected, the concentrated human urine EPO reference standard gives a band pattern similar to a normal human urine sample.

66. The sample of urine from an Epogen® treated individual was clearly positive under the WADA testing criteria. If a person is treated with Epogen®, the pattern clearly shows two sets of bands: the normal bands and the bands due to Epogen®. The density and location of the bands that overlap with the Epogen® bands, however, reveal that the sample came from an individual who was using recombinant human EPO. This is the basis for the WADA urine test for the presence of rHuEPO in human urine.

67. The unpurified CCM from Amgen's recombinant EPO-producing cells shows that Amgen's unpurified EPO starting material as it is produced by mammalian cells grown in culture does not possess any EPO glycoforms that are more acidic than the isoforms found in the purified Epogen® pharmaceutical product.

68. My experiment also reveals that the other recombinant EPOs are somewhat different from Epogen®. The Chinese EPOs are most similar to Epogen®. On close inspection there is a faint band 6. The products from India, Korea, Argentina, and Mexico have more prominent bands 6 and 7. The Mexican product (Epomax) in lane 10 is missing or has fainter bands 1-4. When compared to Epogen®, none of the other recombinant EPO pharmaceutical products have any additional acidic isoforms that are lacking from Epogen®.

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.