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 RESPONSE TO AMGEN'S BENCH MEMORANDUM TO PRECLUDE ROCHE FROM INTRODUCING TESTIMONY OF DR. LONGMORE THAT IS CONTRARY TO THE COURT'S PRIOR ORDERS REGARDING SAFETY, DOSING, UNDISCLOSED FDA COMMUNICATIONS, AND WHETHER MIRCERA CONTAINS HUMAN EPO

The expected testimony of Dr. Longmore that the biological and pharmacological properties of Roche's MIRCERA product is relevant to whether Roche's MIRCERA product is different from any of Amgen's claimed products, and is materially changed from the product of any of Amgen's claimed processes. It is also relevant to both the doctrine of equivalents and the reverse doctrine of equivalents with respect to the substantiality of the differences between MIRCERA and the claimed products. Some of these issues are exactly the same as those to which Amgen's expert Dr. Benet is currently testifying and for which Amgen intends to offer testimony from Dr. Torchilin. Amgen incredulously strains to connect Dr. Longmore's testimony to previous rulings relating to safety and efficacy and discovery relating to Roche's FDA communications.

Amgen makes the spurious argument that a prior ruling on Amgen's motion relating to safety and efficacy issues precludes *all testimony relating to biological and pharmacological differences relevant to infringement.* On the contrary, Amgen's motion sought no such relief and indeed could not have as Amgen is currently offering testimony on these very issues. Amgen's motion was confined to safety and efficacy benefits rather than the functional differences regarding how MIRCERA operates in the body that are so germane to infringement. For instance, Dr. Longmore's expected testimony on dosing schedule is a separate topic from safety or efficacy and not subject to the Court's previous ruling.

In order to obtain FDA approval, Roche had to demonstrate, through clinical studies in the BLA, that MIRCERA's safety profile was comparable and non-inferior to those of the currently available ESAs. In addition, Roche had to establish that MIRCERA was non-inferior in terms of efficacy to the currently available ESAs. Major components of this evaluation included the percentage of patients requiring blood transfusions, the percentage of patients whose hemoglobin was able to be adequately maintained, and the hemoglobin stability rates among patients taking MIRCERA compared to patients taking the currently available ESAs. In terms of efficacy, Roche had to demonstrate non-inferiority irrespective of any dosing schedule; i.e., Roche had to prove to the FDA that Mircera was non-inferior in efficacy to the currently available ESAs regardless of whether Mircera was administered once a week, once every two weeks, or once every four weeks. Put simply, dosing schedule is wholly separate from the concept of efficacy.

Dr. Longmore's expected testimony will address the significant differences between MIRCERA and the asserted claims; differences at the heart of Roche's infringement case in chief. These biological and chemical differences are highly relevant to both 35 U.S.C. § 271(g)

analysis[1] and analysis under the doctrine of equivalents[2] and reverse doctrine of equivalents and have nothing to do with any safety or efficacy discussion. The inherent biological and chemical differences between MIRCERA and the currently available ESAs cause MIRCERA to have a different half-life and dosing schedule than recombinant human EPO. It is those inherent differences that Dr. Longmore will testify to.

Both parties have experts who have offered opinions regarding the safety and efficacy of MIRCERA as shown in the clinical trials, and that testimony has been excluded by the court. Dr. Longmore's expected testimony, however, goes not to any determination of safety or efficacy, but, rather, to biological and chemical differences between MIRCERA and the product of the asserted claims. This is at the heart of the infringement inquiry in this case.

Amgen cannot claim that they are at all prejudiced by Dr. Longmore's expected testimony. Roche has provided Amgen fulsome discovery on dosing schedule, including thousands of pages from Roche's BLA and original data from Roche's clinical trials that contain extensive information on dosing. Some of these documents are among the exhibits Roche disclosed for Dr. Longmore and were produced many months ago in discovery. Amgen has taken Dr. Longmore's deposition and has had his expert report for several months and cannot claim to be prejudiced by his expected testimony.

Amgen, in its bench memorandum, cites to its Motion *In Limine*, to preclude Roche from claiming during the infringement case that MIRCERA does not comprise human EPO in

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[1] *See Eli Lilly & Co., vs. American Cyanamid Co., et. al.*, 66 F. Supp. 2d 924, 928 (D. Ind. 1999) ("[U]nlike cefaclor, compound 6 cannot be taken orally. Oral activity is important because a drug that must be administered by injection requires a hospital visit or a doctor's appointment, but an oral antibiotic can be taken easily at home. This convenience not only makes oral antibiotics more desirable commercial products, but it lowers the costs associated with medical care. . . . There is little dispute that cefaclor has significantly different biological properties from compound 6. Because Opos' additional processing steps 'change the physical or chemical properties of the product in a manner which changes the basic utility of the product,' compound 6 has been materially changed.")

[2] *See Genentech, Inc. v. Wellcome Foundation Ltd.*, 29 F.3d 1555, 1568-1569 (Held that difference in half-life and affinity for binding meant results achieved were not substantially the same; judgment of infringement based on doctrine of equivalents reversed.)

purported contradiction to the Court's summary judgment finding of infringement on claim 1 of the '422 patent. That motion was granted only insofar as the claim may relate to claim 1 of the '422 patent. Moreover, the Court explicitly left open to Roche the ability to argue reverse doctrine of equivalents.[3] As to claim 1 of the '422 patent, Roche has and will continue to abide by the Court's ruling.

Roche has consistently, with the Court's approval, argued that MIRCERA does not contain human EPO with regards to the other asserted claims and Amgen has certainly been on notice of this argument. It can claim no prejudice to any further arguments by Roche. In fact, Amgen's own expert, Dr. Lodish, repeatedly admitted that CERA (the active ingredient in MIRCERA) is not -- and indeed cannot be -- produced in a vertebrate cell, mammalian cell or CHO cell. (Lodish 2505:12-18, 2506:7-14, 2507:17-20, 2508:22-23). Dr. Lodish also stated that CERA is not recovered from a cell culture. (Lodish 2506:15-18). Further, Dr. Lodish admitted that the amino acid sequence contained in Roche's MIRCERA product is not the same as the "amino acid sequence of EPO isolated from urine."

Finally, Dr. Longmore will not be testifying to the specific documents discussed in Amgen's Motion *In Limine* to exclude evidence and argument regarding Roche's FDA filings and communications which the Court held need not be produced during discovery. (D.N. 856, Granted 9/24/07). Amgen's reference to Dr. Longmore's opinion relating to FDA certification as evidence that CERA is a new chemical entity does not rely on any of the documents which were the subject of Amgen's previous motions.

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[3] Electronic ORDER entered granting [1251] Motion in Limine" Motion allowed as to (2) and as to (1) only insofar as the claim may relate to claim 1 of the '422 patent. Moreover, it is still open to Roche to argue reverse doctrine of equivalents should there come to be evidentiary support for such a conclusion." 10/2/07

Dated: October 15, 2007
Boston, Massachusetts

Respectfully submitted,
F. HOFFMANN-LA ROCHE LTD,
ROCHE DIAGNOSTICS GMBH, and
HOFFMANN-LA ROCHE INC.

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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). Pursuant to agreement of counsel dated September 9, 2007, paper copies will not be sent to those indicated as non registered participants.

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