UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

DECLARATION OF BETTE A. GOLDMAN IN SUPPORT OF AMGEN INC.'S OPPOSITION AND MEMORANDUM TO ROCHE'S MOTION TO DISMISS UNDER RULE 12(b)(1) AND (6)

I, Bette A. Goldman, declare:

1. I am a Senior Consultant with the Biologics Consulting Group, Inc. Biologics Consulting Group ("BCG") provides national and international regulatory and product development advice on the development and commercial production of biotechnological and biological products. I joined BCG in May 2005.

2. Prior to joining BCG, I have held various positions within the Food and Drug Administration ("FDA"). From November 2001 to April 2005, I was a Special Assistant and then Associate Director for Regulatory Policy in the Office of Vaccines Research and Review (OVRR), Center for Biologics Research and Evaluation ("CBER") within FDA. My responsibilities included the development, interpretation, and implementation of policy, and advising senior level OVRR staff on regulatory and policy issues.

3. From June 1995 to November 2001, I served in the Office of Therapeutics Research and Review (OTRR), CBER as Associate Director for Regulatory Policy. My Office was responsible for regulating recombinant proteins such as erythropoietin. In that capacity, I served as an advisor to the Office Director to assist in establishing, analyzing and evaluating FDA policies and procedures, and issues regarding the development and licensure of biological products. During my tenure as Associate Director of OTRR, I was the lead on the Fast Track Guidance to Industry which laid out in detail the FDA's definition of products that meet significant unmet medical needs in serious conditions. I was also involved in the writing of a number of guidances related to the Prescription Drug User Fee Act (21 U.S.C. § 301 *et seq*.) ("PDUFA") which established timelines for review.

4. From February 1993 to June 1995, I was a Medical Reviewer for OTRR/CBER, charged with evaluating clinical protocols, proposals of pre-IND packets, and clinical trial design issues. From January 1988 to February 1993, I reviewed Investigational New Drug Applications (INDs) as a Clinical Trials Reviewer/Nurse Consultant in CBER.

5. During my 17 years with FDA, I received a number of awards and citations for my service, including the FDA Award of Merit (1994), the FDA Commissioner's Special Citation (1993), the FDA CBER Center Director's Policy Development Award (1999), and the Health and Human Services Secretary's Award for Distinguished Service (2001and 2005).

6. I was awarded my Bachelor of Arts from George Washington University, my Bachelor of Sciences in Nursing from Catholic University of America in Washington, D.C., and my Masters in Public Health from the Johns Hopkins Bloomberg School of Public Health.

7. As a consequence of my work with FDA, as well as the subsequent experience I have gained at BCG by providing regulatory advice and information to pharmaceutical companies, I am knowledgeable about FDA requirements for the approval of new biologic drugs, as well as FDA practices and policies regarding the review of applications to market and sell these new drugs.

8. I have reviewed the Defendants' Memorandum in Support of Its Motion to Dismiss for Lack of Subject Matter Jurisdiction and Failure to State a Claim for Which Relief Can Be Granted (Defendants' Memorandum) and the Declaration of Iris Kingma-Johnson and provide the following comments.

9. I note that the Defendants' Memorandum makes multiple references to a 22-25 month period for product approval. For example, at page 1 of the Defendants' Memorandum, Defendants state that "If everything proceeds smoothly, and CERA's application follows the average time for new drug approval in recent years, it will take about 22-25 months for CERA to gain approval." They again make this type of assertion at page 7.

10. While the references that Defendants cite to support this time frame indeed show this time range, I believe that this time frame does not accurately reflect the time frame in which FDA could review or approve the Biologics License Application ("BLA") for the defendants' pegylated EPO product for the following reasons: (1) the documents on which the Defendants rely do not distinguish between truly new applications (previously unreviewed by FDA) and re-filed applications (applications which were previously withdrawn or not approved by FDA); (2) the documents on which Defendants rely refer to a much shorter time for review and approval for Priority Applications; (3) the documents on which Defendants rely do not distinguish between the sponsors who have filed the applications (for example, companies like Roche with established, experienced regulatory departments, as compared to companies that do not have this type of resource available to it); and (4) the documents on which Defendants rely do not distinguish between applications for drugs developed to treat medical conditions for which FDA has already approved products, as compared to conditions where there are no generally accepted clinical endpoints.

11. As to my first point, by way of background, PDUFA or the "Prescription Drug User Fee Act" (21 U.S.C. § 301 *et seq*.) was enacted in 1992, and has been subsequently amended in 1997 and 2002. The Act, as amended in 2002, provides at section 502 that "the prompt approval of safe and effective new drugs and other therapies is critical to the

improvement of the public health . . .” and provides for additional funding to “expedite” the drug review process. 21 U.S.C. §379(g). As a consequence of the Act and the program resulting from it, FDA has promulgated performance goals to measure whether it is acting consistent with the general goals articulated in PDUFA. *See,* PDUFA Reauthorization Performance Goals and Procedures[1] (attached to my Declaration as Exhibit 1). FDA’s current goal is to review and take a first action on 90% of all “Standard” new drug applications (including BLAs) in ten months and 90% of all “Priority” new drug applications in six months.[2] In practice, as reported in FDA’s most recent Performance Report to the President and The Congress (for Fiscal Year 2004)[3] (an excerpt of which is attached to my Declaration as Exhibit 2), FDA has met its performance goals 100% of the time for 2003 and 2004 for both Priority and Standard applications.[4]

12. FDA’s first action can include approval of the application, the issuance of an “approvable” letter or a denial of the application (“not approvable”). In addition, the applicant may choose to withdraw its application during this review period. In 2004 (the most recent period for which FDA has reported data), for “Priority” Applications, about 55% of new applications were “approved” in their first action, about 35% of new applications were designated “approvable” in their first action, and about 10% of the new applications were designated “not approvable” or “withdrawn.” *See,* “White Paper Prescription Drug User Fee Act (PDUFA)” by FDA[5] at 6 (attached to my Declaration at Exhibit 3). For “Standard” applications, again about 10% of all new applications were designated either “not approvable” or

[1] *See* http://www.fda.gov/oc/pdufa/pdufaIIIGoals.html.

[2] *See* Exhibit 1 at page 1.

[3] *See* http://www.fda.gov/ope/pdufa/report2004/2004PerformanceReport.pdf.

[4] Exhibit 2 at page 7.

[5] *See* http://www.fda.gov/oc/pdufa/whitepaper11-10/whitepaper11-10.html

"withdrawn."[6] Of the remaining 90% of the new applications filed, over 20% were approved in their first action and greater than 60% were designated "approvable."

13. Thus, while each application is treated as unique, based on the most recent information available from FDA, the Defendants have a greater than 90% chance of receiving an "approvable" or "approved" letter in its first action (with a greater chance of receiving an "approved" letter than an "approvable" letter) if their BLA is treated as a Priority Application and a greater than 80% chance if its BLA is treated as a Standard Application. This likelihood of gaining approval is supported by FDA's Report to the President and the Congress that the median time to approval for new applications (including BLAs), as compared to all applications, is 13.8 months for Standard applications and 6.4 months for "Priority" applications.[7]

14. As to my second point, while I note that at page 7, footnote 6 of their Memorandum, Defendants state that "CERA has been given Standard review status," I find this representation confusing. FDA practice is to discuss and decide at its first internal meeting after receipt of a BLA whether the application should be treated as a "Standard" or "Priority" application. As I understand it, at the time Defendants filed their Memorandum, they had not yet filed their BLA. Thus FDA would not have had such meeting and Defendants would not have received their official review designation to know that their BLA "had been given" Standard review status.[8]

15. "Priority" status is granted to applications by FDA when the new drug is demonstrated to provide significant improvement in the treatment of a condition. Examples of such improvements that can support a grant of Priority status include evidence of superior effectiveness, evidence of improved patient compliance (which could include factors such as

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[6] Exhibit 3 at page 7.

[7] Exhibit 3 at 6.

[8] While FDA may have indicated that Defendants' BLA may be given "Standard" status at a pre-BLA filing meeting, a final determination of an application's status is generally not made until after the BLA is filed and FDA has an opportunity to look at all of the data in context.

whether the drug is easier to use based on storage and dosing schedules), reduction of a treatment limiting drug reaction, or evidence that the new drug can treat patients who are not benefiting by existing therapies. Without reviewing Defendants' data and BLA, it is impossible for me to predict whether their BLA will be granted priority status. However, taking the statements the Defendants make at pages 4 and 5 of their Memorandum regarding their pegylated EPO product, CERA, to be true, there is basis to believe that FDA could designate Defendants' BLA a Priority Application.

16. As to my third point, while FDA treats all BLAs the same, based on my experience, it is my opinion that companies having established, experienced regulatory departments are more likely to submit a quality BLA application to FDA in the first instance than companies that do not have experience in filing regulatory applications with FDA. It thus follows that, all other things being equal, these more experienced companies likely enjoy a higher and faster rate of approval of their BLA. This opinion is supported by a report commissioned by FDA entitled "Independent Evaluation of FDA's First Cycle Review Performance – Retrospective Analysis Final Report" at page iii (*see also,* page 10) attached to my Declaration as Exhibit 4.

17. Likewise, in my experience, if there are accepted clinical endpoints with the disease state to be addressed, such as here in the case of treatments for anemia associated with chronic renal failure, it is more likely that an application will be complete and reviewed more quickly since both FDA and the applicant understands the clinical endpoints that must be met and the showing that must be made to support product approval and have appropriately designed the clinical trials to look at these clinical endpoints.

18. Based on FDA's treatment of "new" BLAs under PDUFA III, it is my opinion that, assuming that Defendants' BLA is designated a "Standard Application," they should expect a first action in 10 months. As I understand it, Defendants filed their BLA for their pegylated

EPO product, CERA, on April 19, 2006.[9] Based on this date, the Defendants could obtain approval by February 2007 if approved in a first action, and by July 2007 if FDA acts consistent with the most recently reported median time to approval for new BLA applications.

19. Assuming that the Defendants' BLA is given "Priority Application" status, they should expect a first action in 6 months and, applying FDA's 2004 approval percentages, there is a greater than 50% chance that the application will be approved. Based on the Defendants' April 19, 2006 filing date, Defendants could obtain approval by the end of October 2006, and by mid-November 2006 if it takes the median time to approval for new Priority Applications.

20. Although legal actions between companies were not an area of my expertise at FDA, in my observation pending litigation should not prevent approval of Defendants' BLA, regardless of whether it is treated as a Standard or Priority Application

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Signed this 24th day of April, 2006.

/s/ Bette A. Goldman
Bette A. Goldman

[9] The filing of a BLA for a new product is the culmination of years of research and development and is the basis for FDA allowing the drug to be marketed. By filing a BLA, Roche is essentially representing to FDA that it believes that its pegylated EPO product is safe and efficacious to treat humans, and that its manufacturing process and its product's characteristics are ready to be inspected by FDA and therefore finalized for marketing. *See* 21 U.S.C. § 355.