EXHIBIT 3

IN THE UNITED STATES DISTRICT COURT
FOR THE 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-12237 WGY

CONTAINS RESTRICTED ACCESS BLA/IND CONFIDENTIAL INFORMATION

SUBJECT TO PROTECTIVE ORDER

FOURTH EXPERT STATEMENT OF RICHARD A. FLAVELL, PH.D. IN RESPONSE TO VARIOUS ARGUMENTS RAISED BY AMGEN'S EXPERTS

disease. This example fully supports my opinion, expressed elsewhere, that small changes in proteins can have a remarkable impact on a protein's function.

76. Finally, Dr. Lodish places a great deal of emphasis on the Court's use of "such as" in its construction for the claim term "human erythropoietin," suggesting that this definition is broad enough to encompass several different polypeptides. As I explained previously, this broadening is contrary to Amgen's admissions during claim construction, and as outlined in my earlier report, is inconsistent with arguments made before the patent office in support of allowance of certain claims.

77. And, even if the Court agrees with Dr. Lodish that the claims are broad enough to cover other erythropoietins, the one thing the Court gives as the claimed sequence is urinary EPO. Like DNA, a protein is a complex chemical having a explicit sequence that defines its identity. I have been told that DNA sequences cannot be conceived until the sequence is in hand. I suspect that a similar situation is true for protein sequences. If so, any such other erythropoietin sequences have not been identified and cannot be within the scope of the invention.

78. In summary, none of the opinions presented by Dr. Lodish changes my prior opinion that claims of the asserted patents are invalid for indefiniteness and lack of written description.

V. PURIFICATION STEPS AFTER ISOLATION ARE SUBSTANTIAL PROCEDURES THAT CONSTITUTE A MATERIAL CHANGE

79. As I explained in my previous expert report, I generally disagree with the contentions of Dr. Lodish concerning purification steps for erythropoietin. I reiterate my prior opinion that purification of erythropoietin sufficient to create a claimed pharmaceutical composition is not disclosed in the patent specification, and that purification steps undertaken after isolation of erythropoietin from cell culture medium constitutes a material change to the product of Amgen's

claimed process. My opinion remains the same. However, I respond below to specific arguments raised by Dr. Lodish in his Supplemental Expert Report on this topic.

80. Dr. Lodish appears to confuse my position regarding "isolation" and "purification."[84] His report states that "[a]ll isolation or purification in a biological process is a matter of degree."[85] I disagree with this statement. Dr. Lodish's observation that EPO has been "'separated' from the 'growth medium, cellular lysates or cellular membrane fractions'" is fully consistent with my definition for EPO found in a crude isolate. This crude isolate has been recovered from many different kinds of material, but has not undergone additional steps to purify EPO – to increase its specific activity by maximizing the concentration of EPO molecules per unit of protein in a sample. This is purification. It is complex, substantial, and, if successful, results in a material change to the crude isolate first recovered.

81. Dr. Lodish states that the product of the claimed process is "far from a 'crude isolate' preparation" because, according to Amgen expert Dr. Bradshaw, "approximately 30% of the total protein is comprised of EPO."[86] I disagree. In my opinion, the most accurate way to describe such a mixture of proteins is a crude isolate. The identity of the remaining 70% of proteins – the majority of protein in the sample – is unknown and uncharacterized. In my opinion, this any preparation with 70% unknown material is crude.

82. Dr. Lodish's criticism of Roche's experts' use of the term "crude isolate" is without import. Regardless of how one of skill would characterize the product of the claimed process, it must still be subjected to further purification involving several discrete steps before it can be a

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[84] *Id.* at ¶ 94.
[85] *Id.*
[86] *Id.* at ¶ 97.