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-12237 WGY

DECLARATION OF WILLIAM L. JORGENSEN, Ph.D. IN SUPPORT OF DEFENDANT'S OPPOSITION TO AMGEN'S MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT OF '422 CLAIM 1, '933 CLAIM 3, AND '698 CLAIM 6

1. I, William L. Jorgensen, Ph.D., submit this Declaration in support of Roche's Opposition to Amgen's Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6. My opinions and analysis submitted in this Declaration were previously disclosed in my expert report submitted in this litigation.

2. I have been the Whitehead Professor of Chemistry at Yale University since 1990. There are roughly 17 tenured professors in the Yale chemistry department. An endowed professorship such as the Whitehead Professorship is held by only of few of the tenured professors. I am one of the few who hold such an honor.

3. I received my A.B. in Chemistry in 1970 from Princeton University. I was awarded a Ph.D. in Chemical Physics in 1975 from Harvard University, where I studied under Elias J. Corey, the 1990 recipient of the Nobel Prize in Chemistry. Professor Corey is a synthetic organic chemist; this is a person who specializes in making new organic molecules (molecules that include at least one carbon atom) and in developing the chemical reactions to facilitate such work. Synthetic organic chemists are critical in drug discovery, as they are the people who work in a laboratory and make organic chemicals, which are the basis for most drugs.

4. After my post-graduate period at Harvard, I joined the chemistry faculty at Purdue University as an Assistant Professor in 1975. I was promoted to Associate Professor with tenure in 1979 and to full Professor in 1982. I was head of the Organic Chemistry Division at Purdue from 1984 - 1987. Between 1985 and 1990, I was the Herbert C. Brown Professor of Chemistry, an endowed position. In 1990 I accepted the position at Yale as the Whitehead Professor of Chemistry, a position I still hold today.

5. My research interests are very broad, covering aspects of physical chemistry, organic chemistry, biochemistry, and pharmaceutical chemistry. A central activity is the use of

principles from physics to computationally model organic and biochemical systems that have relevance to drug discovery, which is the goal of pharmaceutical chemistry. Historically, most drugs have been organic molecules consisting of 20-50 atoms other than hydrogen. However, there has been increasing interest in developing much larger drug molecules such as proteins.

6. We develop and apply computational tools to study the binding of drugs and potential drugs to proteins. This enables us to design new organic molecules that may become drugs. We then often synthesize (meaning prepare by chemical reactions) the potential drugs in our laboratory and we work with biologists to evaluate their activity in inhibiting the target protein and/or in living systems. Ongoing work in my laboratory includes the design and synthesis of anti-HIV, anti-cancer, and anti-inflammatory agents. I have published over 300 articles in refereed journals and hundreds of meeting abstracts, many examining the properties and reactivity of organic molecules, and drug design and discovery. I have presented more than 500 invited lectures on these topics.

7. I have been involved in research on biomolecular systems, which includes proteins and nucleic acids, for 20 years. The work has addressed many aspects of the computer modeling of biomolecules. A fundamental issue is the mathematical representation of biomolecules. The biomolecules are viewed as collections of atoms. The interactions between the atoms are represented by energy expressions, which then control all aspects of the "molecular modeling" of the biomolecular systems including structures, dynamics, and properties. My research group is well known for its work in developing energy expressions that are widely used for modeling water, organic, and biomolecular systems.

8. Our publications in this area are extraordinarily highly cited; for example, a paper of mine from 1988 (J. Am. Chem. Soc., 110, 1657), which addresses modeling proteins, was

celebrated in 2000 as one of the 125 most cited papers in the 125-year history of the Journal of the American Chemical Society. We have also applied the methodology that we have developed in numerous seminal studies, for example, on modeling the denaturation (unfolding) of proteins, the folding of proteins from extended structures, protein-ligand binding, and enzymatic reactions. We reported one of the earliest studies of a simulation of a protein in water, where the water was represented as thousands of discrete water molecules, at the 1988 Nobel Symposium, which is an annual event preceding the Nobel prize awards ceremony.

9. Each year a select number of scientists are invited to the Nobel Symposium, to give presentations on their work in areas of science where breakthroughs are occurring. A dominant activity in my laboratory since that time has been the computational modeling of proteins and protein-ligand complexes. Our combined knowledge of organic chemistry and the biochemistry of proteins provides the foundation for our success in rational drug design.

10. I have consulted for many pharmaceutical companies, including Pharmacia, Agouron, Parke Davis, and Pfizer, principally on improving their drug discovery processes through computational methods. I have served on the Scientific Advisory Boards of several companies, including Evans & Sutherland Inc. and CombiChem Inc. Currently, I am on the Scientific Advisory Boards of Rib-X Pharmaceuticals Inc., Ariad Pharmaceuticals Inc., and Schrödinger Inc., a company that specializes in development and marketing of computer software to aid drug discovery. In 2001, colleagues at Yale and I were the principal scientific founders of Rib-X Pharmaceutical Inc., a biotech company in New Haven, Connecticut that specializes in the design and development of antibacterial agents. I remain actively involved with Rib-X, which now has more than 50 employees and has several compounds in human clinical trials. A key part of their technology is based on my drug-design software.

11. A key example of software that I have developed is the program QikProp, which provides predictions of properties of organic molecules including drugs with molecular weight under about 1200 Daltons. When the structure of a molecule is entered into this program, it makes predictions on items of pharmaceutical interest such as solubility in water, cell permeability, brain/blood distribution, and primary metabolites. Such information is of great relevance for evaluating a compound's potential to be, for example, a drug that can be administered orally rather than intravenously, or a drug that can enter the brain. QikProp has been licensed by Schrödinger Inc. to more than 150 pharmaceutical and biotech companies.

12. I have taught courses in general and advanced Organic Chemistry, Statistical Mechanics, and Computational Chemistry and Biochemistry. Organic chemistry focuses on the properties and reactivity of carbon compounds; statistical mechanics provides the basis for our computer modeling of molecules; computational chemistry and biochemistry center on the application of computers and principles of physics to problems in chemistry and biochemistry.

13. Among my professional affiliations, I am a member of the American Chemical Society, American Physical Society, American Association for the Advancement of Science, the International Society for Quantum Biology and Pharmacology, and the World Association of Theoretical & Computational Chemists. In 1986, I was awarded the Annual Medal of the International Academy of Quantum Molecular Sciences in recognition of my contributions to the field of Computational Chemistry. In 1990, I was a recipient of the Arthur C. Cope Scholar Award from the American Chemical Society (ACS), and in 1998 I received the ACS Award for Computers in Chemical and Pharmaceutical Research.

14. In 2004, I was honored with the Sato Memorial International Award from the Pharmaceutical Society of Japan and the award in Computational Biology from the International

Society for Quantum Biology & Pharmacology. Members of the latter society are interested in the use of computational methods including quantum mechanics to study problems in biology and pharmaceutical chemistry.

15. In 2007, I was elected as a Member of the American Academy of Arts and Sciences. I am and have been the editor for several scientific journals and treatises: *Encyclopedia of Computational Chemistry, Journal of Computational Chemistry, Journal of Chemical Information and Computer Sciences, Journal of Chemical Information and Modeling,* and *Journal of Chemical Theory and Computation.* I have been on the Advisory Board for the Elsevier journal "Bioorganic and Medicinal Chemistry" for many years. I have served as Vice President and, subsequently, President of the International Society for Quantum Biology and Pharmacology from 2000 - 2002. I was also the Chairman of the Computers in Chemistry Division of ACS around the same period.

16. Between 2001 and 2004, I was a member of the National Institutes of Health Medicinal Chemistry study section. Currently, I am on the Advisory Board for the National Institutes of Health's Centers for Chemical Informatics, as well as on the Mathematical & Physical Sciences Advisory Committee for the National Science Foundation. For more than 30 years my research programs have been well supported by numerous agencies. I currently have research support from the National Science Foundation, the National Institutes of Health (National Institute of General Medical Sciences and the National Institute of Allergy and Infectious Diseases), the National Foundation for Cancer Research, the Defense Advanced Research Projects Agency, and Alliance for Lupus Research (ALR). The mission of the ALR is to find better treatments and ultimately cure sytemic lupus, a debilitating autoimmune disease.

17. Attached hereto as Exhibit A is my curriculum vitae.

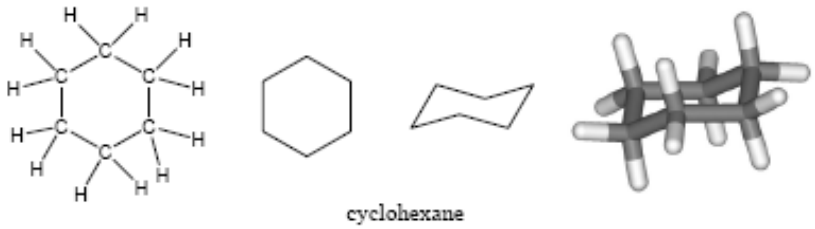
I. BACKGROUND PRINCIPLES IN CHEMISTRY

A. Molecular Structure

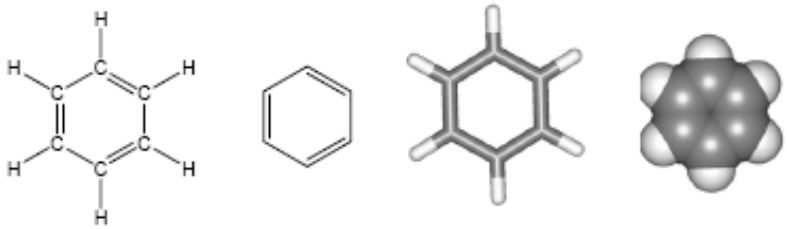
(1) There Are Different Ways to Draw Chemical Structures

18. Molecules are formed when groups of atoms are joined to one another by chemical bonds. It is the arrangement of these atoms and bonds that ultimately determine the 3-dimensional structure of a molecule. The structure of an organic molecule can be drawn or depicted in different ways. The figure below shows 2 molecules, cyclohexane and benzene, each depicted in 4 different ways. The 4 structures in each case would be recognized by chemists as depicting the same molecule. The left-most structure for cyclohexane reflects that the molecule has 6 carbon atoms and 12 hydrogen atoms and shows how they are bonded to each other. However, it does not convey the actual 3-dimensional shape of the molecule. This 3-D shape is best represented by the stick rendering on the far right, where the white tips of the sticks are the hydrogen atoms.[1] The middle drawings for cyclohexane are simplified by not showing the hydrogen atoms; the hydrogens in such drawings are implicit. The six carbons are indicated by the points where the lines meet. These drawings can be made rapidly by a chemist and are often sufficient for discussing or designing reactions.

[1] Such structures for small molecules have been well established through experimental methods such as X-ray crystallography (described in more detail in the section "Experimental Determination of Macromolecular Structures", below).



cyclohexane



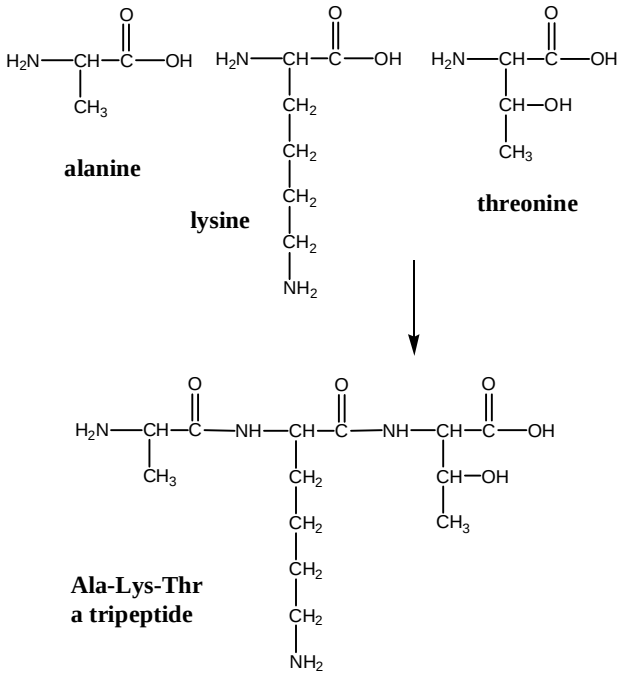
benzene

The right-most structure for benzene is called a "space-filling model"; it emphasizes that molecules are not made of sticks, but rather that electrons are delocalized about the nuclei in "electron clouds". It should also be realized that molecules are, of course, very small. The typical length of a C-H or C-C bond is 1.0 to 1.5 Angstroms, where 1 Angstrom = 0.000000004 inch.

(2) Protein Composition and Structure

19. The large organic molecules that are at the heart of biochemistry are collectively called "biomolecules". Proteins are biomolecules that are built up of one or more polypeptide chain(s). For purposes of convenience, scientists sometimes represent proteins as linear sequences of amino acid residues. In reality, however, proteins are not linear; they are 3-dimensional entities.

20. In nature, there are 20 commonly occurring amino acids that have different side chains; three are illustrated below -- alanine, lysine, and threonine (or Ala, Lys, Thr, in shorthand). Seemingly small variations in these side chains change the identity of the amino acid altogether and can significantly affect the structure, properties and activity of a protein.



21. The OC-N bonds between the amino acid residues in the backbone of a protein are called amide (pronounced "am-id") bonds. Amide bonds are unusually strong. As noted in the Cram & Cram text, "The most stable of the carboxylic acid derivatives is the amide." (Ex. 99, Cram & Cram, "The Essence of Organic Chemistry," Addison-Wesley Publishing Co. 1978, at 273).[2] The OC-N bond, which is formally a single bond, is strengthened owing to a phenomenon known as "resonance" such that in addition to the normal strength of a C-N single bond there is "40% double-bond character in the C-N bond". (Ex. 99 at 274).

22. As a consequence, if one wants to break an amide bond, harsh conditions are required -- typically use of a strong acid like sulfuric or hydrochloric acid and heating at about 100 °C (Celsius) or 212 °F (Fahrenheit), the temperature at which water boils. (Ex. 99 at 276).

[2] All numbered exhibits cited herein are attached to the Declaration of Keith E. Toms In Support Of Defendant's Opposition To Amgen's Motion For Summary Judgment Of Infringement Of '422 Claim 1, '933 Claim 3, And '698 Claim 6.

In addition to breaking amide bonds, such harsh conditions will break most other types of C-N or C-O bonds, and will cause most molecules to almost completely degrade.

(3) Hydrophobic Effect

23. This aggregation of water-fearing (or "hydrophobic") organic molecules in water is an example of the "hydrophobic effect". Essentially, molecules that do not want to interact with the water in their environment will cluster together, so that less of their surface area will be exposed to the surrounding water. One visible example of the hydrophobic effect is the separation of oil and water, or of oil and vinegar in an unshaken bottle of salad dressing. The hydrophobic effect is also considered to be the principal driving force behind the folding of proteins into compact 3-dimensional structures.

24. Specifically, the structure of proteins in the body is not an extended snake-like structure or random coil. Instead, the hydrophobic effect favors an arrangement in which the more hydrophobic regions of the molecule aggregate in a "hydrophobic core", while the more water-loving (or "hydrophilic") regions of the protein have more contact with water. As a result, most biologically important proteins have a relatively well defined 3-dimensional structure or conformation; this is also known as the "native state" or folded state of the protein. However, proteins do undergo molecular oscillations as excursions from the native state.

(4) Non-Bonded Interactions.

25. There is a range of interactions between atoms and molecules that occur in all phases of of matter -- solids, liquids, and gases. "Non-bonded" or "non-covalent" interactions occur between molecules and represent weaker forces than covalent bonds. However, they are still important in determining the properties of materials. For example, strong non-bonded interactions between water molecules make water a liquid at room temperature, while the weaker

interactions between methane molecules cause methane to be a gas at room temperature. The principal types of non-bonded interactions are electrostatic interactions, hydrogen bonding, and van der Waals interactions.

26. Electrostatic interactions occur between atoms that have electric charges. These can be full charges as in the salt sodium chloride, which is written as $Na^{+}Cl^{-}$ to emphasize the full +1 charge on sodium and -1 charge on chlorine. The loss and gain of electrons can also be partial. For example, the electronegativity (or level of attraction for electrons) of oxygen is only a little greater than for nitrogen, so in an N-O bond the oxygen is a little negatively charged, while the nitrogen is a little positively charged. This can be symbolized as $N^{\delta+}$-$O^{\delta-}$ where the δ means that it is a partial charge.

27. Hydrogen bonding is fundamentally just electrostatic attraction; it primarily involves electrostatic interactions X-H …Y where X and Y are nitrogen or oxygen atoms. Nitrogen and oxygen are much more electronegative than hydrogen, so N-H and O-H bonds are significantly "polarized" with partial negative charges on N and O and positive charges on H. Consequently, the N-H…N, O-H…O, N-H…O, and O-H…N interactions can be relatively strong and are called "hydrogen bonds". However, they are still about 10-times weaker in energy than O-H or N-H covalent bonds. Thus, water can form "hydrogen bonds" HOH … OH_2. This hydrogen bonding between water molecules is a key factor in why water for its size has high melting (0 °C) and boiling (100 °C) points. Methane has similar molecular weight, but it melts at -183 °C and boils at -162 °C because it cannot form hydrogen bonds. Hydrogen bonds between amides can also be particularly strong: O=C-NH … O=C-NH. Such interactions are common within proteins and other biomolecules.

28. Even when there is no significant polarization of bonds and/or no dipole moment, there are still weak electrostatic interactions owing to instantaneous fluctuations in the electron clouds for the molecules. These are called van der Waals interactions. For example, when two nitrogen molecules are close, the constantly changing electron clouds adjust on average so that there is a small net attraction between the molecules. For larger molecules, the van der Waals interactions can add up so that the boiling points for alkane liquids increase by about 35 °C per carbon, e.g., the boiling points for butane, pentane, hexane, heptane, and octane are 0, 36, 69, 98, and 126 °C.

(5) Experimental Determination of Macromolecular Structures

29. One of the greatest scientific achievements of the last roughly 60 years has been the determination of the structures of large biomolecules, including proteins and nucleic acids, by X-ray crystallography. The technology stems from work at the beginning of the 20th century on the scattering of X-rays by crystals of simple materials, such as salts that form well ordered crystals. By analysis of the patterns made by the reflected X-rays, one can work backwards and determine the 3-dimensional arrangement of atoms in the crystal. The problem becomes more complicated for crystals of molecules such as proteins that form less ordered arrays in their crystals and that have significant spaces between the molecules containing water and small ions.

30. For many reasons, it is often difficult to get macromolecules to form crystals at all, let alone crystals that diffract well enough to allow accurate structure determination. It is often necessary to test a wide range of crystallization conditions that may be far from physiological. Ultimately, a successful diffraction study yields a map of the electron density distribution for the protein. It is essential to have separately determined the amino-acid sequence for the protein and then to fit the amino acids into the electron density map.

31. Inevitably some uncertainties remain, especially for flexible regions of macromolecules, which may not yield well-defined electron density. Hydrogen atoms are also not located in the X-ray structures.

32. A more recent alternative to X-ray crystallography is the use of nuclear magnetic resonance (NMR) spectroscopy. The principal advantage of NMR is that crystals are not needed; the measurements are made for the protein in aqueous solution. The disadvantages are that it is difficult to obtain structures for proteins with greater than roughly 200 amino acid residues and a larger quantity of purified protein is required. NMR stems from the fact that some atomic nuclei including protons and isotopes of carbon, nitrogen and phosphorus have a magnetic moment or "spin". The energy of radiation required to "flip" these spins in a magnetic field provides information on the structural environment of the nuclei, and more advanced "2-dimensional" techniques provide information on the distances between nuclei.

33. Again, working backwards with enough interatomic distance information for a protein with a known sequence can lead to a model for the 3-dimensional structure of the protein. The models are often not unique, i.e., there are several solutions that fit the distance information comparably well. It is also possible that the search of possible solutions has been inadequate and a better solution has been missed.

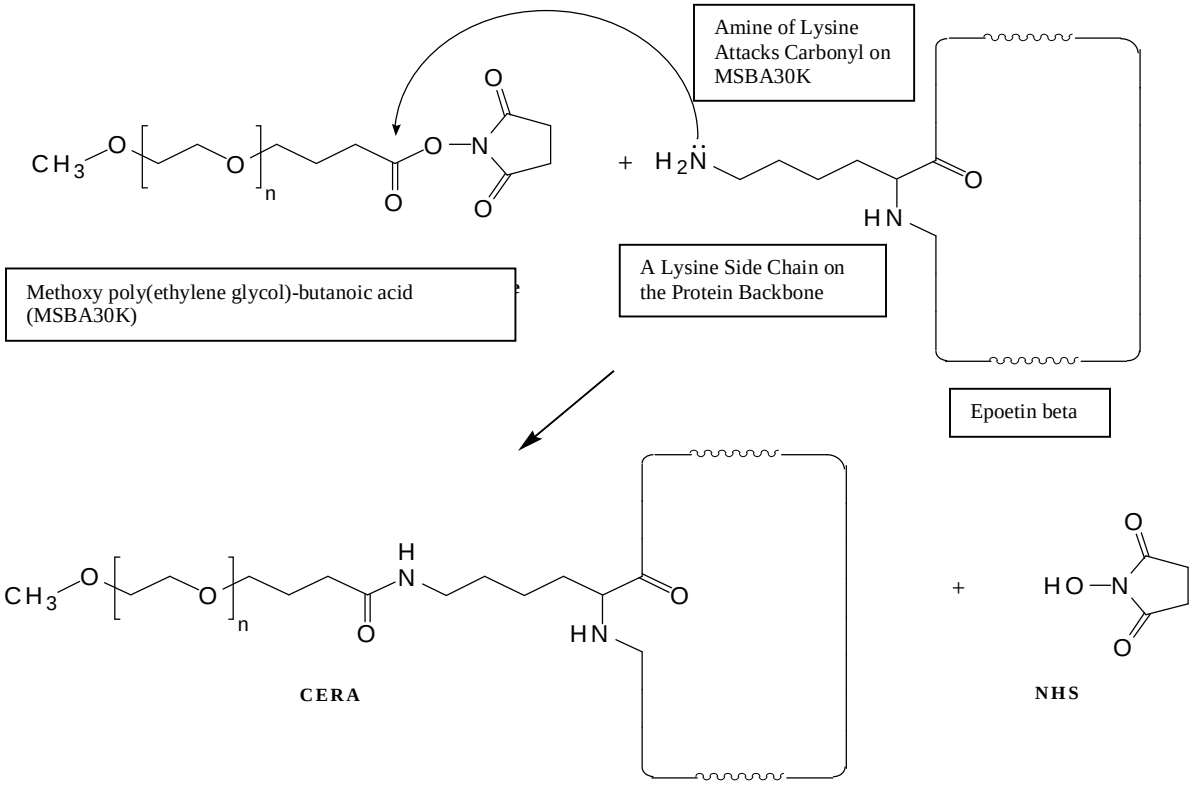
34. Nevertheless, though rough agreement between crystal structures and NMR structures for many protein have been reported (with average deviations of ca. 1-2 Å for atomic positions), X-ray diffraction is considered to be the more reliable technique. In my lab's own computational work on proteins, we have always started with a high-resolution (less than 3.0 Å) X-ray crystal structure.

II. ROCHE'S CERA IS A NEW CHEMICAL ENTITY

A. Pegylation During Synthesis of CERA Results in a New Chemical Entity

35. In order to consider the structure of Roche's CERA drug molecule, it is useful to have some familiarity with the pegylation reaction used in its synthesis. By way of background, I provide a schematic here similar to the illustration in the MIRCERA® BLA.

36. In this reaction, the starting materials epoetin beta and methoxy-30kDa PEG-SBA ("MSBA30K") are converted into a new molecule, CERA. A CERA molecule functions as a single entity, not in parts; it is a new molecule that is roughly twice the size of the starting reagent epoetin beta.



37. The polyethylene glycol molecule used as a starting material in the chemical reaction that produces Roche's drug substance CERA is a particularly reactive ("activated") polyethylene glycol reagent, specifically the N-hydroxysuccinimidyl ester of the methoxy poly(ethylene glycol)-butanoic acid (MSBA30K).

38. The chemical reaction that produces CERA is a nucleophilic addition/elimination where a "nucleophile" (in this case an amino group in the epoetin beta starting reagent) reacts with an "electrophile" (in this case the MSBA30K starting reagent). This reaction forms two new molecules: CERA and N-hydroxysuccinimide ("NHS" - a molecule commonly used in the synthesis of polypeptides).

39. The chemical reaction forms a new bond – an amide bond, in this case. The starting materials, epoetin beta and MSBA30K, are consumed so they no longer exist after this reaction. The covalent bonding between a polyethylene glycol reagent and a protein reagent results in a new molecule with a very different structure -- including thousands of additional atoms and bonds -- than the epoetin beta starting reagent.

40. It is not possible to selectively reverse the pegylation process used in the synthesis of CERA, i.e., to selectively destroy the new covalent bond (a strong amide bond) and get back the reactants. The only option would be to destroy essentially all of the amide bonds. For polyamides and proteins this can be achieved by treatment under harsh conditions such as by using hydrochloric acid at 100 °C for 24 hours. This harsh treatment is unselective and can be expected to break most of the amide bonds in the substrate, leading to severe degradation; an analogy can be drawn to taking a piece of crystal and shattering it beyond recognition.

B. <u>Binding Affinity of CERA With the EPO Receptor</u>

41. As a result of its differences in structure and composition, CERA is well documented to have very different properties from EPO. One such difference is the binding affinity of CERA vs. EPO with the EPO receptor.

42. Binding affinity is a critical consideration in drug development, and can make the difference between success and failure in the search for a pharmaceutically useful compound.

43. Roche experiments have found that CERA has a 50- to 100-fold lower binding affinity than EPO. Even if the binding affinity for CERA with the EPO receptor is assumed to be 50-fold lower than that for EPO, this means the K_{eq} ($1/K_d$) for CERA is 50-fold smaller than for EPO binding to the EPO receptor. When dealing with pharmaceuticals this difference is very large.

44. Binding affinity is a measure of how strongly a drug molecule binds to its receptor. Only when the active component in a drug like MIRCERA® binds to its receptor can the drug cause the desired therapeutic effect. Therefore, all else being equal, binding affinity profoundly affects the dose of a drug needed in order to cause the desired biological effect. For example, if Drug B has a 50-fold lower binding affinity than Drug A, it would be expected that Drug B must be given at a dose that is 50 times higher than the effective dose of Drug A in order to get the same biological response. Therefore, if Drug A (like some commonly used antibacterials) were dosed at 1 gram per day, Drug B would have to be given at doses of 50 grams per day. Such a dosage is impossibly high, and would render Drug B pharmaceutically useless. From a drug discovery perspective, therefore, the difference in binding affinity between CERA and EPO is strikingly significant.

45. As further detailed below, the greatly different binding affinities of CERA vs. the epoetin beta starting reagent with the EPO receptor also reflect that CERA and epoetin beta differ significantly in 3-dimensional structure.

III. ARTIST'S RENDERINGS CITED BY AMGEN DO NOT PROVIDE ACCURATE INFORMATION ABOUT THE STRUCTURE OF CERA

46. I have reviewed the 2006 Lancet article by Iain Macdougall (Ex. 229, Macdougall & Eckardt, *Novel strategies for stimulating erythropoiesis and potential new treatments for anaemia*, Lancet, 2006, 368:947-953), which was shown to me by Amgen's counsel at my

deposition. The caption to Figure 3 in Macdougall ("Figure 3") states that the Figure "represents an artist's view of the possible structures for epoetin and CERA." (Ex. 229 at 949). An identical illustration appears in the Roche document designated by Amgen as Exhibit 31 to its "Memorandum In Support of Amgen Inc.'s Motion for Summary Judgment Of Infringment of '422 Claim 1, '933 Claim 3, And '698 Claim 6." Neither document in which this drawing appears cites any data to support it. Based on my extensive experience with computer modeling programs, and consistent with that statement that this drawing is merely an "artist's view"(Ex. 229 at 949), it is my opinion that this illustration reflects little more than imagination.

47. The structures and interactions of CERA have never been directly elucidated experimentally, e.g., via X-ray crystallography or nuclear magnetic resonance (NMR). In fact, the detailed structure of CERA cannot be determined with these, or any other known methods. In the most basic terms, the molecule is constantly moving, and does not stay still long enough for a clear image to be captured. As a result, no experimentally determined coordinates have been reported for CERA and no modeling tools are available to provide reliable images of such large, complex structures.

48. In the absence of experimentally derived images, however, it is still possible to make some predictions about the structure of the CERA molecule based on its known properties. These properties, particularly the weaker binding (*e.g.*, 50-100 fold) of CERA than EPO to the EPO receptor, are inconsistent with a structure having a polyethylene glycol "tail", separate and away from the rest of the molecule, such as is depicted in Figure 3.

49. The significantly weaker binding affinity with the EPO receptor of CERA vs. EPO indicates that, contrary to what is depicted in the artist's rendering in Figure 3, CERA cannot have a polyethylene glycol chain that is away from the rest of the molecule, so as to be

uninvolved in CERA's binding to the EPO receptor. If such a structure were correct, then binding affinity with the EPO receptor would be identical for CERA and for epoetin beta. As noted above, this is not the case. On the contrary, the difference in EPO receptor binding affinity of CERA vs. EPO is very large.

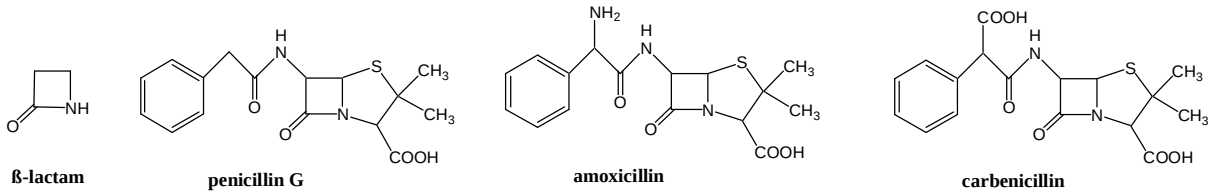
50. Moreover, the difference in EPO-receptor binding affinity between CERA and EPO cannot be explained by the hypothesis that certain isoforms of CERA are inactive. While it is true that a small adjustment would be needed if some forms of CERA (different pegylation sites) were inactive, this adjustment would not account for such a large discrepancy in binding affinity. As a purely hypothetical example, if 50% of the CERA molecules in a mixture were inactive, the binding affinity for CERA would be 2x (or 2-fold) less than for EPO. The actual difference in binding affinity to the EPO receptor between CERA and EPO (50- to 100-fold) is far too great to be explained by inactivity of certain forms of CERA molecules. The clear explanation is that the structures of CERA and the CERA-EPO receptor complex are very different than for EPO.

51. In order to illustrate a more likely structure for CERA -- one that is consistent with CERA's known properties -- I provide the attached example (attached to this declaration at Exhibit B) that resulted from work with my biomolecular modeling program MCPRO. (Ex. 214, Jorgensen and Tirado-Rives *Molecular Modeling of Organic and Biomolecular Systems Using BOSS and MCPRO*, Comput. Chem. 2005, 26, 1689-1700). The starting point was an NMR structure for EPO, which was retrieved from the Protein Data Bank. About 680 ethyleneoxy units were then added around the EPO in a similar manner to adding solvent molecules; they were relaxed in a Monte Carlo statistical mechanics simulation, and then they were linked to form the polyethyleneoxy chain attached to the EPO N-terminus. The energetics of the system

are described by my OPLS energy functions, which are one of the standards in biomolecular modeling. The system is not fully equilibrated and it contains no water or ions. However, in my opinion, the illustrated structure is reasonable and is consistent with the observed properties of CERA including the reduced antigenicity, longer half-life, and reduced binding affinity for the EPO-receptor in comparison to EPO. Concerning the latter, the illustrated structure is consistent with a greater reorganization penalty for CERA than EPO to achieve a binding geometry for the EPO-receptor.

IV. THE TERM "PEG-EPO" IS MERELY JARGON

52. I note finally that nomenclature provides no information about the presence of a material change of CERA over epoetin beta. "Peg-EPO", like many terms in chemistry, is merely jargon, used by chemists as a shorthand way to refer to the products of any number of pegylation reactions. For example, an entire class of antibacterial drugs is often referred to as β-lactams because they contain a β-lactam ring. An early member was penicillin G; it had to be administered intravenously and had a relatively narrow spectrum of activity.



ß-lactam penicillin G amoxicillin carbenicillin

53. Extensive research led to many improved β-lactams that were subsequently approved as drugs. Examples include amoxicillin, which can be administered orally and is effective against a wide range of infections, and carbenicillin, which has an even broader spectrum of activity. Each molecule is unique and acts as a whole. Scientists understand that referring to all of these compounds as β-lactams is merely jargon and in no way implies that these compounds do not show profound differences in efficacy and practical utility. In

comparison to the β-lactam example, the structural differences between CERA and EPO are simply vast. The term "peg-EPO" is used purely as a matter of convenience.

54. Products of peglyation reactions involving protein reagents and PEG reagents are new molecules with very different properties than their starting materials. No chemist seeing the term "peg-EPO" would assume that this term guaranteed any properties or activities of the new molecule. Moreover, the term "peg-EPO" is highly imprecise and could refer to a huge number of possible products of such a reaction, all of which can have very different properties. It is therefore my opinion that this term is simply jargon, and is not indicative of the properties of any of the many different molecules to which it refers.

55. Nor would a chemist think that the term indicated that the new molecule could be divided into parts or "moieties" in some meaningful way. Chemists know that molecules function as a whole, not in parts, and that small changes in molecular structure can have dramatic effects on activity. This term does not provide any meaningful information about the structure or properties of CERA.

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

DATE: June 28, 2007

/s/ William L. Jorgensen
William L. Jorgensen, PH.D.

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/ Keith E. Toms
Keith E. Toms

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