

United States District Court,  
D. Delaware.

**NOVO NORDISK A/S and Novo Nordisk Pharmaceuticals Inc,**  
Plaintiffs.

v.

**ELI LILLY AND COMPANY,**  
Defendant.

**ELI LILLY AND COMPANY,**  
Counterclaim Plaintiff.

v.

**NOVO NORDISK A/S, Novo Nordisk Pharmaceuticals Inc., and Novo Nordisk of North America, Inc,**  
Counterclaim Defendants.

No. Civ.A. 98-643 MMS

**Nov. 18, 1999.**

Edward M. McNally, and Gretchen Ann Bender, of Morris, James, Hitchens & Williams, Wilmington, Delaware, Robert Schaffer, Robert C. Sullivan, Jr., Ira Jay Levy, Joseph R. Robinson, and Patricia J. Clarke, of Darby & Darby P.C., New York, New York; for Plaintiffs and Counterclaim Defendants, of counsel.

Richard L. Horwitz, Joanne Ceballos, and William J. Dorgan, Potter Anderson & Corroon, LLP, Wilmington, Delaware, R. Danny Huntington, B. Jefferson Boggs, Jr., William L. Mathis, Nhat D. Phan, Matthew P. Blischak, and Rel S. Ambrozy, of Burns, Doane, Swecker & Mathis, LLP, Alexandria, Virginia; for Defendant and Counterclaim Plaintiff, of counsel.

### ***MEMORANDUM OPINION***

**SCHWARTZ, Senior J.**

#### **I. Introduction**

Novo Nordisk A/S and Novo Nordisk Pharmaceuticals, Inc. (collectively "Plaintiffs") filed a complaint and amended complaint against Eli Lilly and Company ("Eli Lilly" or "Lilly") seeking a declaratory judgment that Lilly's U.S. Patent No. 5,474,978 ("the '978 patent"), entitled "Insulin Analog Formulations," is invalid, unenforceable, and not infringed by Novo Nordisk. Lilly counterclaimed against Plaintiffs and Novo Nordisk of North America, Inc. (collectively "Novo Nordisk" or "Novo") for infringement of the '978 patent.

The parties disagree on the scope and meaning of certain claim language. Pursuant to *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996), the Court now construes the scope and meaning of the disputed claim language in the '978 patent.

## II. Factual Background

### A. History of Insulin and Insulin Analogs

The '978 patent relates generally to insulin and insulin analogs and their use in the treatment of diabetes mellitus. Human insulin ("hI" or "insulin") is a naturally occurring human protein that performs the function of transporting sugar molecules from blood to cells where the sugar is needed for energy. Insulin is made up of 2 polypeptide chains (chain A and chain B) joined together by covalently bound FN1 atoms of sulfur ("S").FN2

FN1. A "covalent bond" is "a non-ionic chemical bond formed by shared electrons." Merriam-Webster's New Collegiate Dictionary 300 (10th ed.1998).

#### FN2. Human Insulin

Animals and humans having a deficiency of insulin suffer from a disease known as diabetes mellitus. They are dependent on injections of insulin to help regulate their blood sugar levels. However, it is difficult for diabetics to time these injections to avoid unhealthy fluctuations in blood sugar level, resulting in conditions known as hyper- and hypo-glycemia. Frequent fluctuations over the course of a lifetime can lead to long term complications such as hardening of the arteries, kidney failure, blindness, coma, and death.

Until the 1980's, human diabetics relied on injections of bovine, and other animal, insulin. In the 1980's, scientists developed methods to genetically engineer human insulin. This was a major advancement since hI works much better in humans than animal insulin. In solutions of pure hI, most of the molecules of hI exist as monomers, i.e., single molecules of hI. However, in that solution, the monomers of hI tend to rapidly form large, covalently bound polymers with one another. These polymers render the solution biologically inactive because hI will only act in the body in its monomeric form. It is very difficult for the covalently bound polymers to break apart and separate into monomers. Thus, solutions of monomers of hI have a very short "shelf life," making them impractical for diabetic treatment.

Scientists later discovered that, if zinc ions are added to the solution, the hI molecules tend to aggregate into hexameric association states, each containing six hI molecules and two zinc ions. In each association state, the zinc ions and the hI molecules are held together by weak intermolecular forces that are weaker than intramolecular covalent bonds.FN3 Scientists have analyzed the conformation, or shape, of a Zn-hI hexamer and refer to the shape of this conformation as  $T_6$ . When the hI molecules are in these hexamer association states, the rate at which hI molecules form polymers is much slower than the rate at which monomers of hI form polymers. Therefore, solutions of hI, where the most of the hI molecules are in hexamer association states, have a much longer shelf life than solutions of hI where most of the hI molecules are monomers.

FN3. In contrast, the polymers of hI are held together by strong covalent bonds.

Scientists next discovered that, if zinc ions and phenolic derivatives are added to the solution of pure hI, the hI molecules aggregate into slightly different hexamer association states, each containing six hI molecules,

two zinc ions, and three or more phenolic molecules. The scientists analyzed the conformation of the Zn-phenolic-hI hexamer association state and discovered that it is different from the  $T_6$  conformation of the Zn-hI hexamer association state. Scientists refer to the conformation of the Zn-phenolic-hI hexamer association state as  $R_6$ .FN4 The rate at which hI molecules in  $R_6$  association states form polymers is about the same as the rate at which hI molecules in  $T_6$  association states form polymers and is much slower than the rate at which monomers of hI form polymers. Therefore, solutions of hI, where the most of the hI molecules are in  $R_6$  association states, have a much longer shelf life than solutions of hI where most of the hI molecules are monomers.

FN4. The hI molecules can also aggregate into a hybrid  $T_3R_3$  hexamer conformation, where three molecules of hI have a T conformation and three molecules of hI have a R conformation.

However, hI molecules will only act in the bloodstream to transport sugar when they are monomers, and not aggregated into hexamers. Thus, when solutions containing  $T_6$  or  $R_6$  hexamers are injected into the body, the hexamers must disassociate, releasing monomers of hI into the bloodstream. Scientists discovered that the  $T_6$  and  $R_6$  hexamer association states take almost one hour to fully dissociate into monomers once injected into the body. Therefore, it is difficult for patients to time injections to coincide with the peaks of blood sugar after eating a meal.

To attempt to solve this problem, scientists developed human insulin analogs (hIA) which are hI molecules with one or more of the amino acids either altered or deleted.FN5 The idea was to create hIA's that would perform the same blood sugar transport function as hI, but that would resist aggregation into hexamers so as to avoid the problem with long dissociation times. Scientists engineered at least twelve different hIA's that transport blood sugar as effectively as hI. As scientists predicted, these hIA molecules do not aggregate into stable hexamer association states either by themselves or in the presence of zinc ions. However, these hIA monomers have the same problem as monomers of hI. The molecules tend to rapidly form biologically inactive polymers. Thus, solutions of hIA monomers, like solutions of hI monomers, have a very short shelf life.

FN5. The hIA's have special shorthand abbreviations. If an amino acid is substituted it is shown by the abbreviation of the new amino acid with its position as a superscript. For example, Asp<sup>B28</sup>-hI means that Asp has been substituted as a new amino acid at position 28 on the B chain. If an amino acid is deleted, it is represented by "des" followed by the position deleted. For example, des(B27)-hI means that the amino acid at position 27 in the B chain has been deleted.

## **B. The '978 Patent**

The specification of the '978 patent teaches the following. The inventors sought to solve the problem of solutions of hIA monomers tending to rapidly form covalently bound polymers by trying to make hIA molecules aggregate into weakly bound, stable, hexameric association states. Scientists already knew that the hIA molecules would not aggregate into hexamers by themselves or in the presence of zinc ions. The inventors were able to make the hIA molecules form stable hexamer association states by adding both zinc ions and phenolics to solutions containing pure hIA.

Each hexamer association state is composed of six molecules of hIA, two zinc ions, and at least three molecules of phenolics, held together by weak intermolecular forces, weaker than covalent bonds. The inventors analyzed the conformation, or shape, of the Zn-phenolic-hIA hexamer association state and discovered that it is different from the T<sub>6</sub> conformation of the Zn-hI hexamer association state and the R<sub>6</sub> conformation of the Zn-phenolic-hIA hexamer association state.

Moreover, solutions containing mostly Zn-phenolic-hIA hexamers have all of the advantages of solutions containing mostly hI hexamers, without the disadvantages. The hIA molecules in the Zn-phenolic-hIA hexamers tend to form polymers at a very slow rate (about the same rate as hI molecules in T<sub>6</sub> and R<sub>6</sub> hexamers), giving the solution a long shelf life. Also, the Zn-phenolic-hIA hexamers tend to dissociate into monomers of hIA at a much faster rate than do the T<sub>6</sub> and R<sub>6</sub> hexamers of hI. Thus, solutions of hIA hexamers have more rapid action than solutions of hI hexamers.

The '978 patent has thirteen claims directed to this invention, three of which are independent.FN6 Independent claims 1 and 12 claim a "human insulin analog complex." Dependent claims 2-8 claim a "parenteral pharmaceutical formulation comprising the human insulin analog complex of claim 1." Dependent claims 10-11 claim a method of using a "pharmaceutical formulation containing the composition of claim 1." Independent claim 13 claims a "parenteral pharmaceutical formulation."

FN6. The full text of the claims is:

1. A human insulin analog complex, which comprises: six molecules of a human insulin analog, two zinc ions, and at least three molecules of a phenolic derivative selected from the group consisting of m-cresol, phenol, or a mixture of m-cresol and phenol; such that the insulin analog complex is a hexamer; wherein the human insulin analog is human insulin wherein Pro at position B28 is substituted with Asp, Lys, Leu, Val, or Ala, and Lys at position B29 is Lys or Pro; des(B28-B30)-human insulin; or des (B27)-human insulin.
2. A parenteral pharmaceutical formulation comprising the human insulin analog complex of claim 1.
3. The parenteral pharmaceutical formulation of claim 2, which further comprises an isotonicity agent.
4. The parenteral pharmaceutical formulation of claim 3, which further comprises a physiologically tolerated buffer.
5. The parenteral pharmaceutical formulation of claim 4, wherein the buffer is sodium phosphate.
6. The parenteral pharmaceutical formulation of claim 5, wherein the isotonicity agent is glycerol.
7. The parenteral pharmaceutical formulation of claim 6, wherein the phenolic derivative is m-cresol.

8. The parenteral pharmaceutical formulation of claim 7, wherein the human insulin analog is Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin.

9. A human insulin analog composition of claim 1, wherein the human insulin analog is Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin.

10. A method of treating a patient suffering from diabetes mellitus, which comprises administering to said patient a pharmaceutical formulation containing the composition of claim 1.

11. The method of claim 10, wherein the human insulin analog is Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin.

12. A human insulin analog complex, consisting of: six molecules of insulin analog, two zinc ions, and at least three molecules of a phenolic derivative selected from the group consisting of m-cresol, phenol, or a mixture of m-cresol and phenol; such that the insulin analog complex is a hexamer; wherein the human insulin analog is human insulin wherein Pro at position B28 is substituted with Asp, Lys, Leu, Val, or Ala, and Lys at position B29 is Lys or Pro; des(B28-B30)-human insulin; or des(B27)-human insulin.

13. A parenteral pharmaceutical formulation consisting of: about 3.5 mg/mL Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin, about 19.7  $\mu$ g/mL zinc, about 7 mM sodium phosphate, about 16 mg/mL glycerin, and about 29 mM m-cresol; wherein Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin is a hexamer.

The following claim language is in dispute:

1. "human insulin analog complex" and "complex" (claims 1, 12);
2. "such that the insulin complex is a hexamer," "wherein Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin is a hexamer," and "hexamer" (claims 1, 12, 13);
3. "pharmaceutical formulation" (claims 2-11, 13);
4. "comprises" and "two zinc ions" (claim 1);
5. "consisting of" and "two zinc ions" (claim 12);
6. "wherein the human insulin analog is human insulin wherein Pro at position B28 is substituted with Asp, Lys, Leu, Val, or Ala, and Lys at position B29 is Lys or Pro; des(B28-B30)-human insulin; or des(B27)-human insulin" (claims 1, 12) and the T<sub>6</sub> limitation; FN7

FN7. See, *infra*, Section IV.E for an explanation of the T<sub>6</sub> limitation.

7. "hexamer" (claims 1, 12, 13) and the R<sub>6</sub> limitation; FN8

FN8. *See, infra*, Section IV.E for an explanation of the R<sub>6</sub> limitation.

8. "parenteral" (claims 2-11, 13);

9. "administering" (claim 10);

10. "patient" (claim 10).

### III. Applicable Law for Claim Construction

Patent infringement actions are composed of two phases. First, in the claim construction, or *Markman*, phase, the court determines the scope and meaning of the patent claims as a matter of law. *See* *Cybor Corp. v. FAS Technologies, Inc.*, 138 F.3d 1448, 1454 (Fed.Cir.1998) (en banc) (citing *Markman*, 517 U.S. at 371-73). Second, the claims are compared to the allegedly infringing device. *See id.* In this opinion, the Court concerns itself only with the claim construction phase.

The proper construction of claims is based primarily on the intrinsic evidence: the claim language, the specification, and the prosecution history. *See* *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1309 (Fed.Cir.1999). FN9 Claims should be construed from the point of view of the person of ordinary skill in the field of the invention at the time of the invention. *See* *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1477 (Fed.Cir.1998).

FN9. Patent claims "particularly point out and distinctly claim the subject matter which the applicant regards as his invention." *Markman*, 116 S.Ct. at 1387-88 (quoting 35 U.S.C. s. 112). The patent specification "describes the invention 'in such full, clear, concise, and exact terms as to enable any person skilled in the art ... to make and use the same.'" *Id.* at 1388. The prosecution history "contains the record of all the proceedings before the Patent and Trademark Office, including any express representations made by the applicant regarding the scope of the claims." *Vitronics Corp. v. Conceptronic Inc.*, 90 F.3d 1576, 1582 (Fed.Cir.1996).

The claim language itself is first and foremost in importance when construing the meaning and scope of the patent. *See* *Smiths Indus. Medical Systems, Inc. v. Vital Signs, Inc.*, 183 F.3d 1347, 1357 (Fed.Cir. July 14, 1999); *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 989 (Fed.Cir.1999). The general rule for interpreting the language of a claim is:

that terms in the claim are to be given their ordinary and accustomed meaning. General descriptive terms will ordinarily be given their full meaning; modifiers will not be added to broad terms standing alone. In short, a court must presume that the terms in the claim mean what they say, and, unless otherwise compelled, give full effect to the ordinary and accustomed meaning of claim terms.

*Johnson Worldwide*, 175 F.3d at 989. Thus, if the claim is unambiguous and clear on its face, the Court need not consider the other intrinsic evidence. *See* *Smiths Indus.*, 183 F.3d at 1357 (citing *Renishaw PLC v. Marposs Societa per Azioni*, 158 F.3d 1243, 1248-49 (Fed.Cir.1998)).

Where the applicability of a common meaning is unclear or where more than one common meaning could be assigned to a claim term, reference to the specification and prosecution history is appropriate to discern the ordinary and accustomed meaning. *See id.* at 1248; *Phillips Petroleum Co. v. Huntsman Polymers Corp.*, 157 F.3d 866, 871 (Fed.Cir.1998) (turning to specification where, at time of invention, the ordinary meaning of term was disputed and two possible meanings were in existence). Thus, "the claims are construed in accordance with the rest of the specification of which they are a part, and not contrary to it." *C.R. Bard, Inc. v. M3 Systems*, 157 F.3d 1340, 1360 (Fed.Cir.1998); *Renishaw*, 158 F.3d at 1250. Indeed, "[t]he construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Renishaw*, 158 F.3d at 1250.

A court engaging in claim construction may enter "a definition of a claim term other than its ordinary and accustomed meaning" in two situations. *Johnson Worldwide*, 157 F.3d at 990. "The first arises if the patentee has chosen to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term" in the specification. *Id.* (citations omitted); *accord Renishaw*, 158 F.3d at 1249. "The second is where the claim term or terms chosen by the patentee so deprive the claim of clarity that there is no means by which the scope of the claim may be ascertained from the language used." *Johnson Worldwide*, 157 F.3d at 990 (citations omitted). "In these two circumstances, a term or terms used in the claim invites-or indeed, requires- reference to intrinsic [evidence beyond the claim language itself] or in some cases, extrinsic evidence to determine the scope of the claim language." *Id.* (citation omitted).

The specification has been described as "often the single best guide to the meaning of a disputed term." *Vitronics Corp. v. Conceptronic Inc.*, 90 F.3d 1576, 1582 (Fed.Cir.1996). When the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term. *See Multiform Desiccants*, 133 F.3d at 1478. At the same time, however, a court "may not read a limitation into a claim from the written description." *Renishaw*, 158 F.3d at 1248; *see also Comark Communications, Inc. v. Harris Corp.*, 156 F.3d 1182, 1186 (Fed.Cir.1998).

In addition, the prosecution history informs the understanding of terms found in both the specification and the claim. *See Multiform Desiccants*, 133 F.3d at 1478. ("The evolution of restrictions in the claims, in the course of examination in the PTO, reveals how those closest to the patenting process-the inventor and the patent examiner-viewed the subject matter."). "Use of the prosecution history to *interpret* claim language is distinct from prosecution history *estoppel*, which is a limitation on the doctrine of equivalents." 5A Donald S. Chisum, *Chisum on Patents* s. 18.03[d][2] (1998) (emphasis in original); *see also Amhil Enterprises Ltd. v. Wawa, Inc.*, 81 F.3d 1554, 1559 (Fed.Cir.1996). In most instances, the prosecution history is cited to refute an overly broad interpretation of a claim term put forth by the patentee. *See, e.g., Multiform Desiccants*, 133 F.3d at 1478.

After examining the intrinsic evidence of the patent, if the meaning of the claim language is still ambiguous, the Court may consider extrinsic evidence, "if necessary to aid the court's understanding of the patent." *See Wright Medical Technology, Inc. v. Osteonics Corp.*, 122 F.3d 1440, 1443 (Fed.Cir.1997). However, "if the meaning of a disputed claim term is clear from the intrinsic evidence-the written record-that meaning, and no other, must prevail; it cannot be altered or superseded by witness testimony or other external sources simply because one of the parties wishes it were otherwise." *Key Pharmaceuticals v. Hercon Labs. Corp.*, 161 F.3d 709, 716 (Fed.Cir.1998). The Federal Circuit has ranked four common forms of extrinsic evidence from most reliable to least reliable: (1) technical treatises and dictionaries; (2) prior art; FN10 (3) expert testimony on technology; FN11 and (4) expert testimony on claim construction.FN12 *See Vitronics Corp. v.*

Conceptronic, Inc., 90 F.3d 1576, 1584-85 (Fed.Cir.1996). In some cases, reference to extrinsic evidence, although not necessary for claim construction, may have a useful confirmatory purpose. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1308 (Fed.Cir.1999).

FN10. The prior art can shed light on how terms have been used by those skilled in the art. *See Vitronics*, 90 F.3d at 1585.

FN11. Expert testimony may help the court understand the underlying technology. *See id.*

FN12. The opinions of experts and inventors on claim construction should be given little, if any, weight in claim interpretation. *See id.*

Finally, if a claim term is still ambiguous, the court should adopt the interpretation that affords more narrow coverage of allegedly infringing devices, so that the claims perform their intended function of giving notice of what is covered to potential infringers. *See Athletic Alternatives, Inc. v. Prince Manufacturing, Inc.*, 73 F.3d 1573, 1581 (Fed.Cir.1996).

#### **IV. Claim Construction of the '978 Patent**

##### **A. Claims 1, 12, and 13 and the definitions of "complex," "hexamer," and "formulation"**

Lilly argues that "complex" (claims 1 and 12) FN13 means "an equilibrium of association species and their free constituents in solution." Docket Item ("D.I.") 156 at 2. It then argues that the terms "complex is a hexamer" (claim 1) and "LysPro-human insulin is a hexamer" (claim 13) mean "nearly all of the human insulin analog in the solution are in the hexameric association state." FN14 D.I. 156 at 2. Lilly also maintains that the term "formulation" does not have any meaning independent of the term "pharmaceutical," *see* Transcript ("Tr.") at 390:24-391:16, and that the phrase "pharmaceutical formulation" (claim 13) means "an aqueous solution formulated to be of appropriate safety and efficacy for treatment of patients." FN15 D.I. 156 at 2.

FN13. Since claims 1 and 12 are identical, except for the use of "comprises" in claim 1 and "consisting of" in claim 12, the meaning of "complex," "hexamer," and "formulation" will be identical for purposes of both claims. *See Digital Biometrics Inc. v. Indentix, Inc.*, 149 F.3d 1335, 1345 (Fed.Cir.1998) (general rule is that same words in claims should be given same meaning). Therefore, for the remainder of the discussion of "complex," "hexamer," and "formulation," unless otherwise indicated, claim 1 will be used as the representative claim for claims 1 and 12. However, the Court notes that it departs from this general rule, as discussed *infra*, because the term "hexamer" means something different in claim 13 than it does in claims 1 and 12.

FN14. Lilly's exact argument is that "such that the insulin analog complex is a hexamer" means "an equilibrium of association species and their free constituents in solution where nearly all of the human insulin analog in the solution are in the hexameric association state." D.I. 156 at 2. When one removes the part of the definition that is identical to the definition of "complex," one is left with the definition of "hexamer" quoted in the text.





that the term "complex" refers to the equilibrium containing molecules and molecular structures and that "complex is a hexamer" (claim 1) and "LysPro-human insulin is a hexamer" (claim 13) means that most of the species in the equilibrium are Zn-hIA structures. Novo agrees that an equilibrium exists and that the Zn-hIA structures exist as part of a larger equilibrium.FN18 Indeed, Novo argues that "formulation" (claims 2-11 and 13) refers to the equilibrium containing the Zn-hIA structures. Thus, the parties agree that the molecular structures, Zn-hIA structures, and equilibrium exist. The dispute centers around whether the claim language is directed to a molecular structure or to an equilibrium.

FN17. For example, Lilly's own definition of "is a hexamer" states that "most of the analog are in the hexameric association state" meaning that most of the hIA molecules are bound together with one another in Zn-hIA structures. D.I. 156 at 3. Also, Lilly's definition of "complex" as "equilibrium of association species and their free constituents in solution" means that the equilibrium contains many molecular structures. D.I. 156 at 2. In addition, in its Opening Brief Lilly argues that in the equilibrium, "nearly all the insulin analog molecules come together in six molecule units," which refers to molecular structures bonding together in Zn-hIA structures. *See* D.I. 156 at 8. Although Lilly argues that these structures exist nowhere in isolation, Lilly does not dispute that they do exist.

FN18. For example, Novo's attorneys admitted that the Zn-hIA structures exist as part of a larger solution or equilibrium. *See* Tr. at 347:22-348:9.

The Court essentially adopts Novo's definition of "complex" and holds that the term "complex," as used in the claims (claims 1 and 12), is an individual molecular structure, i.e., "a chemical association state of two or more molecules held together by non-covalent bonds." FN19 Next, the Court essentially adopts Novo's definition of "formulation" and holds that "formulation," in claims 2-11 and 13, means "an equilibrium containing molecules and molecular structures." Finally, the Court essentially adopts both Novo's and Lilly's definitions of "hexamer," holding that the term "hexamer" means different things in different contexts so that "complex is a hexamer" in claims 1 and 12 and "Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin is a hexamer" in claim 13 mean different things.FN20 In claims 1 and 12, because it is being used in the context of individual molecules and their structure, the term "hexamer" refers to the Zn-hIA structure, i.e. "a type of complex where six molecules of human insulin analog are held together in a single structure." In claim 13, because it is being used in the context of a "formulation," which is an equilibrium, the phrase "LysPro-human insulin is a hexamer" is shorthand meaning "in the equilibrium, most of the LysPro-human insulin molecules are in Zn-hIA structures." Interestingly, at the *Markman* hearing Lilly's expert, Dr. Weiss stated that the term "hexamer" has these two competing definitions, depending on the context.FN21

FN19. As set forth in the text, *infra* pp. 23-27, in the specification, complex refers to both a molecular structure and equilibrium, dependent upon the context. Because of the context of claims 1 and 12, complex refers to a molecular structure.

FN20. The Court recognizes that having two different definitions for "hexamer" violates the general rule of claim construction that the same word should be interpreted to have the same meaning throughout the claims. *See* Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1310 (Fed.Cir.1999). However, "where the language of the written description is sufficient to put a reader on notice of the different uses of a term, and where those uses are further apparent from publicly available documents referenced in the

patent file, it is appropriate to depart from the normal rule of construing seemingly identical terms in the same manner." *Id.* at 1311. When a term has different meanings in different contexts, "the term must be read to correspond only to the plausible meaning in each context." *Id.* As discussed in the test, *infra*, the claim language, the specification and the prosecution history fully support the two meanings of hexamer.

FN21.  
THE WITNESS [Dr. Weiss]: In general the word hexamer is used in two senses in this patent. It refers, if it's not modifying anything, hexamer by itself, it refers to the hexameric self association unit.... If it's modifying hexamer, if it's modifying complex either in the phrase hexamer complex or such that complex is a hexamer in this adjunct title sense, then it means that the equilibrium is such that nearly all the molecules are participating in one of the hexameric self association states.

Tr. at 80:19-81:7. The Court does not rely on this extrinsic evidence in resolving the issues. Nonetheless, it takes some comfort in Dr. Weiss' testimony.

### **1. The Claim Language**

The starting point for claim construction is the plain language of the claims. *See* Smiths Indus. Medical Systems, 183 F.3d at 1357. The claim language provides support for the Court's definitions of "complex," "hexamer," and "formulation."

First, claim 1 defines "complex" in terms of the number of molecules of hIA, the number of ions of zinc, and the number of molecules of phenolic. Because claim 1 refers only to eleven molecules, the term "complex" must refer to only an individual molecular structure, not to an equilibrium. If "complex" referred to an equilibrium, it would have to contain some of the individual molecules of hIA, zinc, and phenolics and some of the Zn-hIA structures. That is, the equilibrium would have to contain more than simply the eleven molecules listed in the claim.FN22 It would not make sense for an equilibrium state to contain only the eleven molecules listed as part of the "complex."

FN22. Lilly argues that the use of the term "comprising" in claim 1 means that the "complex" contains more than the listed eleven molecules in the equilibrium. This argument is unpersuasive for two reasons. First, as discussed in Part IV.C, *infra*, the term "comprising" means that the "complex" can contain other types of molecules not listed, but that it can contain six, and only six, hIA molecules and two, and only two, zinc ions. Second, claim 12 has the exact same claim language as claim 1 except that it uses the closed ended "consisting of" instead of "comprising." This language means that the "complex" in claim 12 contains only the eleven listed molecules. These eleven claimed molecules by themselves could not be an equilibrium between individual molecules and the Zn-hIA structures.

Lilly also argues that the eleven molecules listed in claim 1 refer to the relative stoichiometric proportions of the molecules in the equilibrium. However, if this argument is correct, then Lilly's other definition of "complex is a hexamer" meaning that most of the molecules in the equilibrium are be in Zn-hIA hexamers cannot also be correct. To illustrate, accept for the moment that Lilly is correct. According to Lilly's definitions, claim 1 would then claim an equilibrium having hIA molecules and Zn ions in a 6:2 ratio where most of the molecules in the equilibrium are in Zn-hIA hexamers. However, the patent specification teaches a wide range of ratios of hIA molecules to zinc ions in the equilibrium,FN23 while also teaching that in

each individual hexamer structure there are exactly 6 hIA molecules and exactly two zinc ions. FN24 The fact that the claim recites a whole number ratio of 6:2, as opposed to some fractional ratio, strongly indicates that the claim is directed to the structure, not the equilibrium. Moreover, the most preferred embodiment in the specification teaches that in order to achieve a solution of mostly hexamers, there must be more than two zinc ions for every six molecules of hIA. FN25 Therefore, the list of the eleven molecules in claim 1 does not refer to the stoichiometric ratios of these molecules in an equilibrium. Rather, it refers to the number of molecules in the structure.

FN23. The specification recites a sliding scale range of the preferred concentrations of hIA molecules to zinc ions in order for the solution to have mostly hexamers. *See* '978 Patent at 4:60-67. The preferred range of hIA is from 1.2 mg/mL to 17.5 mg/mL. *See id.* The preferred concentration of zinc is 14 mug/mL to 35 mug/mL. Converting these weights to moles reveals a wide range of ratios of zinc ions per hIA molecules. For these calculations the molecular weight of hIA is estimated at 6000 mg/mmol, *see* 8 McGraw-Hill Encyclopedia of Science and Technology, 264 (8th ed.1997), and the molecular weight of zinc is 65.4 mg/mmol, *see* 19 McGraw-Hill Encyclopedia of Science and Technology, 699. The following calculations illustrate the point:

Smallest Ratio of hIA to Zn:

$$\text{hIA: } (1.2 \text{ mg/mL})(\text{mmol}/6000 \text{ mg}) = 2.0 \times 10^{-4} \text{ mmol/mL}$$

$$\text{Zn: } (35 \text{ mug/mL})(\text{mg}/1000 \text{ mug})(\text{mmol}/65.4 \text{ mg}) = 5.35 \times 10^{-4} \text{ mmol/mL}$$

$$\text{Ratio: } 2.0 \text{ hIA}:5.35 \text{ Zn} = 6.0 \text{ hIA}:16.0 \text{ Zn}$$

Largest Ratio of hIA to Zn:

$$\text{hIA: } (17.5 \text{ mg/mL})(\text{mmol}/6000 \text{ mg}) = 29.0 \times 10^{-4} \text{ mmol/mL}$$

$$\text{Zn: } (14 \text{ mug/mL})(\text{mg}/1000 \text{ mug})(\text{mmol}/65.4 \text{ mg}) = 2.14 \times 10^{-4} \text{ mmol/mL}$$

$$\text{Ratio: } 29.0 \text{ hIA}:2.14 \text{ Zn} = 6.0 \text{ hIA}:0.4 \text{ Zn}$$

FN24. *See* '978 patent at 4:67-5:1.

FN25. Figure 3 illustrates that in order to achieve mostly hexamers, there must be an hIA concentration of 3.5 mg/mL. In this solution, the ratio of Zn ions to hIA molecules is 0.5. *See* '978 Patent at 3:37-38. Thus, the ration of hIA to Zn is 6.0 hIA:3.0 Zn, which is more than 2 zinc ions for every six molecules of hIA.

In contrast, claim 13 defines a "formulation" in terms of the concentrations of the hIA, zinc, and phenolics in solution. Because claim 13 refers to the concentrations in solution, and not the number of molecules, the term "formulation" must refer to the equilibrium containing molecules and molecular structures. Moreover, the proportion of the hIA molecules to zinc ions is not the 6:2 ratio of these species in a single Zn-hIA structure.FN26 Therefore, the term "formulation" must refer to more than just a molecular structure; it must refer to the overall equilibrium.

FN26. Claim 13 claims a ratio of roughly 2.5 zinc ions to 6 hIA molecules.

Because claim 1 claims a "complex," i.e., a molecular structure, the term "hexamer" is used in the structural sense to mean a single Zn-hIA structure. It would make no sense for the claim to read that most of the complexes are in the Zn-hIA molecular structure because the claim only lists the exact number of molecules needed to form one Zn-hIA molecular structure. It follows that "hexamer" is being used in the structural sense.

Because claim 13 claims a "formulation," i.e., an equilibrium, the phrase "Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin is a hexamer" means that most of the Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin molecules are associated into Zn-hIA molecular structures. It would make no sense for "hexamer" to have a structural meaning in this claim because it claims 3.5 mg/mL Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin, or about  $3.5 \times 10^{17}$  molecules per mL of solution. It would be absurd to say that this number of molecules "is a molecular structure." Rather, in the context of a "formulation" or equilibrium, it makes more sense for "hexamer" to have its shorthand meaning as most of the LysPro-human insulin molecules are in Zn-hIA structures.

Lilly counters that, in claim 1, the term "hexamer" cannot refer to a single Zn-hIA structure because the term "hexamer" would be superfluous. It further argues that "hexamer" cannot mean an individual molecular structure of six hIA molecules, two zinc ions, and at least three phenolic molecules because the "complex" is already defined as a molecular structure containing these eleven components. However, Lilly's position cannot withstand close scrutiny because "complex" is a general term referring to all types of molecular structures, including monomers, dimers, tetramers, and hexamers (Zn-hIA structures). As such, the term "hexamer" refers to a specific type of complex where six of the hIA molecules are bound together in a single structure. The term "hexamer" is not superfluous because a "complex, which comprises: six molecules of human insulin analog" could be a complex of three dimers or one hexamer. Therefore, "hexamer" has independent meaning as a complex where the six hIA molecules are bound together in a single structure.

Lilly further argues that "complex" must refer to the equilibrium state because claim 10 claims using a "complex" to treat a patient and a patient can only be treated with an equilibrium solution.FN27 However, claim 10 actually claims using a "formulation" containing the "complex" to treat the patient. Since the "formulation" is the equilibrium, the Court's definitions of "complex" and "formulation" are fully consistent with the use of these terms in claim 10.

FN27. Claim 10 actually recites using the "composition" of claim 1 to treat the patient. However, since the "complex" recited in claim 1 is the only composition of matter recited in claim 1, the term "composition" means a "complex."

For the reasons stated above, the claim language supports the Court's definitions of "complex," "hexamer," and "formulation."

## **2. The Specification**

The above discussion of the meaning of the claim terms is further supported by the specification. The specification supports how the Court interprets the use of "complex," "formulation," and "hexamer" in the claims, including the two meanings of the term "hexamer" dependent on the context in which it is used.

At the outset, the specification uses the term "complex" by itself as a noun, uses the term "hexamer" by itself as a noun, and uses the phrase "hexamer complex" where "hexamer" is an adjective and "complex" is a noun. Much like the term "hexamer," the specification uses the term "complex" to mean either an equilibrium or a structure, depending on the context in which it is used. FN28 In the context of describing the behavior of an equilibrium, and the associated properties of stability and fast action, "complex" is used as shorthand to describe an equilibrium and the term "hexamer" is used as shorthand for the equilibrium where most of the insulin or insulin analog species are aggregated into Zn-hIA structures.FN29 When used outside the context of an equilibrium and in the context of individual molecules and their structures, the term "complex" refers to an individual molecular structure and the term "hexamer" refers to a particular type of molecular structure, the Zn-hIA structure.FN30 Only one sentence in the specification is ambiguous as to whether "complex" and "hexamer" refer to the equilibrium or the molecular structure.FN31 Since claims 1 and 12 only refer to "complex" in the context of individual molecules, the term "complex" is only used in the structural sense in the claims. Thus, the specification fully supports the Court's definitions of "complex" and "hexamer" in the claims.

FN28. *See* n. 19.

FN29. *See* '978 Patent at 2:47-50 ("Brange et al ... disclose that when insulin is administered *as a hexamer* ... the *hexamer* must be sterically more hindered"-in the Brange et al. reference, the authors are discussing the properties of solutions of human insulin where most of the insulin molecules in the solution are in hexamer structures); *id.* at 62-63 ("The present *formulation* is a zinc-phenolic induced *hexamer complex*"-this means that most of the insulin analogs in the formulation are in Zn-hIA structures); *id.* at 63-65 ("The rate of absorption for the *hexamer complex* is at least two times that observed with insulin"-this clause describes the "formulation" and its rapid action); *id.* at 65-66 ("when the *hexamer complex* is formulated, it is equally stable"-this describes stability of the equilibrium); *id.* at 3:3-5 ("when formulated, this *hexamer complex* retains the fast acting properties"-this describes the rapid action of the equilibrium); *id.* at 3:30-41 ("FIG. 3 is a graphical representation of Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin in a *hexamer complex*. The graph is the in vitro dissociation of formulated insulin (o); Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin formulated as a *hexamer complex* ..."-this paragraph describes the behavior of equilibrium formulations of hIA so that hexamer complex is used in the equilibrium sense.); *id.* at 4:33-34 ("Both the zinc and phenolic derivative are critical to achieve a *complex* that is stable and capable of rapid dissociation and onset of action"-this refers to the properties of the equilibrium); *id.* at 5:16-20 ("it is quite surprising that the formulated *hexamer* analog brings a rapid onset of action. Unlike insulin, the formation of an insulin analog *hexamer complex* does not adversely effect the time required to achieve peak serum insulin analog concentration"-these sentences refer to the properties of the equilibrium state.); *id.* at 5:21-31 ("FIG. 1 demonstrates, in human patients, the mean glucose infusion rate response to a formulation containing monomeric Lys<sup>B28</sup>Pro<sup>B29</sup>-hI (formulated without zinc); a formulated Lys<sup>B28</sup>Pro<sup>B29</sup>-hI *hexamer*; and human regular insulin. The formulated *hexamer complex* retains the rapid action of monomeric Lys<sup>B28</sup>Pro<sup>B29</sup>-hI. The absorption rate is significantly more rapid than regular human insulin. Thus, the results in FIG. 1 illustrate: First, *hexamer* Lys<sup>B28</sup>Pro<sup>B29</sup>-hI and monomeric Lys<sup>B28</sup>Pro<sup>B29</sup>-hI have similar rates of absorption; second, both *hexameric* and monomeric Lys<sup>B28</sup>Pro<sup>B29</sup>-hI have faster rates of absorption than insulin"-this paragraph refers to the rapid action and stability of the equilibrium.); *id.* at 5:32-33 ("The formulation comprising the insulin analog *complex* as *hexamer* is stable"-this refers to the properties of the equilibrium); *id.* at 5:40 ("Formulated Lys

B<sup>28</sup> Pro B<sup>29</sup>-hI, as a *hexamer complex*, exhibits diminished rate of higher molecular weight polymer formation"-this refers to the equilibrium and its stability.); id. at 5:67-6:2 ("Samples of Lys<sup>B<sup>28</sup></sup> Pro B<sup>29</sup>-hI as a *hexamer complex* were prepared in an identical fashion except 19.7 mug/ml zinc was added"-this sentence refers to preparation of a solution that is in equilibrium); id. at 6:16-23 ("Degradation is initiated by incubating formulated and unformulated preparations of insulin and monomeric and *hexameric* Lys<sup>B<sup>28</sup></sup> Pro B<sup>29</sup>-hI at 30 (deg.)C. The formulated insulin and *hexamer* Lys<sup>B<sup>28</sup></sup> Pro B<sup>29</sup>-hI contained: 3.5 mg/ml protein, 16 mg/ml glycerol, 7 mM dibasic sodium phosphate heptahydrate, 1.25 mg/ml m-cresol, 1.09 mg/ml phenol, and 0.0245 mg/ml zinc oxide at a pH of 7.3 to 7.4"-this refers to the composition of a solution in equilibrium.); id. at 6:44-45 ("The in vitro dissociation properties of monomeric Lys<sup>B<sup>28</sup></sup>Pro B<sup>29</sup>-hI, Lys<sup>B<sup>28</sup></sup> Pro B<sup>29</sup>-hI as a *hexamer complex*, and insulin are probed using static light scattering." This refers to experiments with a solution in equilibrium.); id. at 7:12-20 ("FIG. 3 discloses the results of the light scattering study. The in vitro dissociation profile of Lys<sup>B<sup>28</sup></sup>Pro B<sup>29</sup>-hI as a *hexamer complex* and insulin are quite different .... the formulations are equally stable against chemical degradation, *hexamer* Lys<sup>B<sup>28</sup></sup> Pro B<sup>29</sup>-hI has a greater propensity to dissociate than insulin"-this refers to experiments with equilibrium solutions).

FN30. *See id.* at Abstract ("The present invention discloses a human insulin analog *complex* and formulations"-differentiates the structure from the equilibrium); id. at 1:61-63 ("The addition of certain metal ions, primarily zinc [to the solution containing insulin], enhance the chemical stability by driving the insulin to form *hexamers*, specifically Zn(II)-T6 conformations"-First, this language differentiates "hexamers" from the equilibrium solution. Also, the plural on the word "hexamer" implies that the hexamer is a single structure and that the solution contains multiple hexamers. Finally, the Zn(II)-T6 conformation is a way of describing the structure of an individual molecular structure ); id. at 1:64-66 ("phenolics have been shown to specifically bind to the insulin *hexamer* and induce an allosteric conformational change"-refers to phenolic molecules binding to the insulin hexamer structure.); id. at 2:5-6 ("insulin, in the presence of zinc, aggregates to form a well defined *zn-hexamer structure*"-this teaches that the hexamer complex is a type of structure.); id. at 2:13-14 ("the highly stable *Zn-hexamer complex*"- this refers further to the Zn-hexamer structure.); id. at 2:26-28 ("The association that is observed with these analogs is ... distinct from the predominate, well-defined, Zn-insulin *hexamers*."-the use of the plural on "hexamer" indicates that "hexamer" is a single structure); id. at 2:31-41 ("In view of the published literature, it is surprising that the present invention affords monomeric insulin analogs in a well defined, stable zinc-phenol *hexamer complex*. This *hexamer complex* is uniquely different from those *complexes* observed with insulin under identical conditions. Insulin *complexes* with zinc and phenol are in a Zn(II)-R<sub>6</sub> conformation. The *hexamer complex* of the present invention is not identical to this conformation. Also quite remarkably, the insulin analog *hexamer complex* has a much greater propensity to dissociate than insulin."-This paragraph discusses the structure of the hexamer complex of the present invention as distinguished from the R<sub>6</sub> structure observed in the prior art complexes containing insulin. Because the R<sub>6</sub> notation and the term "conformation" refer to structure of a single hexamer complex of insulin, *see* Tr. at 197:18-203:23; 209:13-210:4, the patent teaches that "complex" and "hexamer complex" refer to a single structure); id. at 2:45-46 ("the obvious route to creating a fast-acting insulin is to prevent dimer or *hexamer* formation"-this indicates that the goal is to avoid the formation of individual hexamer structures in the equilibrium.); id. at 2:58-59 ("efforts to chemically stabilize the monomeric insulin analog with zinc by forming a well defined, *hexamer complex*," referring to forming a molecular structure.); id. at 3:11-16 ("This invention provides a human insulin analog *complex*, which comprises: six molecules of a human insulin analog, two zinc ions, and at least three

molecules of a phenolic derivative selected from the group consisting of m-cresol, phenol, or a mixture of m-cresol and phenol; such that the analog *complex is a hexamer*."-This sentence defines the "complex" as a molecular structure by defining it in terms of the molecules that are part of the structure. It defines "hexamer" as a particular type of molecular structure.); *id.* at 3:16-17 ("The invention further provides parenteral formulations comprising the *hexamer complex*"-differentiating between the formulation, i.e., the equilibrium, and the hexamer complex in the equilibrium); *id.* at 3:45-46 ("the invention provides a monomeric human insulin analog *complex* as a *hexamer*"- refers to a single molecular structure.); *id.* at 4:30-33 ("The insulin analogs of the present invention *complex* with zinc ions and a phenolic derivative to form a stable, *hexamer conformation*"-here, the term "hexamer" is used to describe the conformation, which generally refers to a molecular structure.); *id.* at 4:60-61 ("The *hexamer complex* may be *formulated* into stable, rapid acting parenteral *formulations*"- differentiates the molecular structure from formulating it into an equilibrium.); *id.* at 4:67-5:1 ("two zinc ions are bound to each *hexamer*"-in this phrase "each hexamer" refers to each of the individual molecular structures in the equilibrium.); *id.* at 5:1-3 ("the *hexamer complex* binds as many as seven phenolics. Generally, when formulated, six phenolics are bound to the *hexamer*."- Here, "complex" and "hexamer" refer to the individual molecular structure because it lists the number of molecules bound to the hexamer structure.); *id.* at 7:17-18 ("both preparations contain *hexameric* association states"-the use of the plural indicates that the hexameric association states refer to individual molecular structures in the solution).

FN31. *Id.* at 4:34-35 ("The *hexamer complex* consists of two zinc ions *per hexamer* of human insulin analog and at least three molecules of a phenolic derivative selected from the group consisting of m-cresol, phenol, or a mixture of m-cresol and phenol.") One could argue that "hexamer complex" refers to the equilibrium and that the second instance of "hexamer" refers to the structure because the "hexamer complex" is composed of "two zinc ions *per hexamer* of human insulin analog," implying that the "complex" contains multiple "hexamers." However, the sentence also states that the "hexamer complex" is composed of "at least three molecules of phenolic derivative," but not *per hexamer*, implying that there are only three molecules of phenolic in the complex and that the complex refers to the structure. Given the ambiguities in the drafting of this sentence and the clear drafting throughout the rest of the specification, the language of this sentence will be ignored for purposes of claim construction.

The specification also supports the Court's definition of "formulation" as the equilibrium. When the specification uses the terms "formulation" or "formulated" it refers to the equilibrium or the rapid action and stability of the equilibrium.FN32 Therefore, as defined above, the "formulation" refers to the equilibrium state.

FN32. *See id.* at Abstract ("invention discloses a human insulin analog hexamer complex and *formulations*"-differentiates between structure and the equilibrium "formulation"); *id.* at Abstract ("formulation [not complex or hexamer] provides rapid onset of action"-discusses the rapid action of the equilibrium); *id.* at 1:14-15 ("various *formulations* with different time-actions have been developed"); *id.* at 1:28-31 ("Recently, considerable effort has been devoted to create insulin *formulations* and insulin analog *formulations* that alter the kinetics of the subcutaneous absorption process"-discusses the rapid action properties of the equilibrium.); *id.* at 1:24-32 ("all commercial pharmaceutical *formulations* of insulin contain insulin in the self associated state and predominantly in zinc-hexamer form."-this sentence states that "formulations" are equilibria which contain the free constituents, insulin and zinc, and the hexamer complexes.); *id.* at 2:65-67 ("when the hexamer complex is *formulated*, it is equally stable"-discusses



stability of equilibrium) *id.* at 3:2-5 ("when *formulated* this hexamer complex retains the fast acting properties" -discusses stability of equilibrium); *id.* at 3:15-16 ("the invention further comprises parenteral *formulations* of the hexamer complex"-the formulation is the equilibrium that contains the complexes); *id.* at 3:36-41 (" *formulated* samples contained [concentrations of solutions]"-the "formulation" is the equilibrium state because it is defined in terms of solution concentrations); *id.* at 3:30-41 ("FIG. 3 is a graphical representation of Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin in a hexamer complex. The graph is the in vitro dissociation of *formulated* insulin (o); Lys<sup>B28</sup>Pro<sup>B29</sup>-human insulin *formulated* as a hexamer complex ..."- This paragraph describes the behavior of equilibrium formulations of hIA.); *id.* at 4:60-61 ("the hexamer complex may be *formulated* into stable, rapid, acting parenteral *formulations*," discussing the equilibrium); *id.* at 5:3 ("when *formulated*, six phenolics are bound to the hexamer"-teaches that the formulation is the equilibrium solution which contains multiple hexamers); *id.* at 4:67-5:1 ("in the *formulation* ... two zinc ions are bound to each hexamer"-teaches that the formulation is the equilibrium solution which contains multiple hexamers); *id.* at 5:8-13 ("An isotonicity agent, preferably glycerin, may be added to the formulation. The concentration of the isotonicity agent is in the range known in the art for insulin formulations, preferably about 16 mg/ml. The pH of the formulation may be buffered with a physiologically tolerated buffer, preferably a phosphate buffer, like sodium phosphate"-this paragraph discusses other ingredients that can be added to the equilibrium.); *id.* at 5:17-18 (" *formulated* hexamer brings on rapid onset of action"-discusses the rapid action of the equilibrium); *id.* at 5:40-44 (" *formulated* Lys<sup>B28</sup>Pro<sup>B29</sup>-hI, as a hexamer complex, exhibits a diminished rate of higher molecular weight polymer formation"-refers to the rapid action of the equilibrium); *id.* at 5:33-34 ("the *formulation* comprising the insulin analog complex is stable"); *id.* at 6:16-23 ("Degradation is initiated by incubating *formulated* and unformulated preparations of insulin and monomeric and hexameric Lys<sup>B28</sup> Pro<sup>B29</sup>-hI at 30 (deg.)C. The *formulated* insulin and hexamer Lys<sup>B28</sup> Pro<sup>B29</sup>-hI contained: 3.5 mg/ml protein, 16 mg/ml glycerol, 7 mM dibasic sodium phosphate heptahydrate, 1.25 mg/ml m-cresol, 1.09 mg/ml phenol, and 0.0245 mg/ml zinc oxide at a pH of 7.3 to 7.4."-This refers to the composition of a solution in equilibrium.); *id.* at 7:12-20 ("FIG. 3 discloses the results of the light scattering study .... the *formulations* are equally stable against chemical degradation, hexamer Lys<sup>B28</sup> Pro<sup>B29</sup>-hI has a greater propensity to dissociate than insulin"-this refers to experiments with equilibrium solutions.).

The term "formulated" refers to a "formulation" where most of the species are in hexamer structures, while the term "unformulated" refers to a "formulation" where most of the species are not in hexamer structures. *See id.* at 30-41 ("FIG. 3 is a graphical representation of the dissociation of Lys<B28>Pro<B29>-human insulin in a hexamer complex. The graph is the in vitro dissociation of *formulated* insulin; Lys<B28>Pro<B29>-hI *formulated* as a hexamer complex; *unformulated* insulin; and monomeric Lys<B28>Pro<B29>-hI monitored by static light scattering at 488 nm at a 90o angle. The *formulated* samples contained 0.5 mol Zn per mol protein, 1.25 mg/ml m-cresol and 1.09 mg/ml phenol, 7 mM sodium phosphate and 16 mg/ml glycerol. The *unformulated* and monomeric samples contained no additional excipients."-This paragraph illustrates how the words formulated and unformulated are used to refer to hexameric and monomeric solutions, respectively); *id.* at 5:36-40 (" *Unformulated* human insulin undergoes a slower rate of polymer formation of 0.61% per week. Upon formulation, however, the rate of high molecular weight polymer formation is reduced to 0.095% per week for insulin"); *id.* at 5:17-18 (" *formulated* hexamer brings on rapid onset of action"); *id.* at 5:40-44 (" *formulated* Lys<sup>B28</sup>Pro<sup>B29</sup>-hI, as a hexamer complex, exhibits a diminished rate of higher molecular weight polymer formation"); *id.* at 5:62-6:2 (" *Unformulated* samples of insulin and Lys<B28> Pro<B29> -hI were prepared at 3.5 mg/ml in 7 mM sodium phosphate, and with or without 1.25 mg/ml m-cresol, 1.09 mg/ml phenol and 16 mg/ml glycerol,

depending on the experiment performed. Samples of Lys<B28>Pro<B29>-hI as a hexamer complex were prepared in an identical fashion except 19.7  $\mu$ g/ml zinc was added."); *id.* at 6:16-23 ("Degradation is initiated by incubating *formulated* and *unformulated* preparations of insulin and monomeric and hexameric Lys<sup>B28</sup> Pro<sup>B29</sup>-hI at 30 (deg.)C. The *formulated* insulin and hexamer Lys<sup>B28</sup> Pro<sup>B29</sup>-hI contained: 3.5 mg/ml protein, 16 mg/ml glycerol, 7 mM dibasic sodium phosphate heptahydrate, 1.25 mg/ml m-cresol, 1.09 mg/ml phenol, and 0.0245 mg/ml zinc oxide at a pH of 7.3 to 7.4."); *id.* at 6:48-50 ("Three *formulated* and *unformulated* protein stock solutions are prepared as described except that the unformulated protein stock solutions did not contain zinc, glycerol, or preservatives [i.e., they do not form hexamers]"). Thus, the specification validates the Court's definitions of "complex," "hexamer," and "formulation."

### 3. The Prosecution History

The next step is to turn to the prosecution history to help understand the terms in the claims. *See* Multiform Desiccants, 133 F.3d at 1478. The prosecution history provides support for the Court's definitions of "complex," "hexamer," and "formulation."

First, the arguments in the prosecution history support that the terms "complex" and "hexamer" have different meanings in different contexts. In the context of describing the behavior of a "formulation," or equilibrium, and the associated properties of stability and fast action, the terms "complex" and "hexamer" are used as shorthand for the equilibrium where most of the insulin or insulin analog species are aggregated into Zn-hIA structures. FN33 When used outside the context of an equilibrium and in the context of individual molecules, the terms "complex," "hexamer," and "hexamer complex" refer to the Zn-hIA structure.FN34 Therefore, the prosecution history supports the two definitions of "complex" and "hexamer." Second, the arguments in the prosecution history support the definition of "formulation" as an equilibrium. FN35 The prosecution history, like the claim language and specification, confirms the Court's definitions of "complex," "hexamer," and "formulation."

FN33. *See* Amendment and Remarks of March 14, 1995, Novo Ex. D at A-370 ("when phenol or m-cresol is added to a zinc solution of a monomeric analog, the monomeric analog forms a well ordered, hexamer association state"-refers to the equilibrium solution.); *id.* ("the *hexamer* association state retains a rapid profile of action"-refers to the properties of the equilibrium.").

The following passage also illustrates how the word "hexamer" is used in the equilibrium sense, to distinguish the prior art based on the predominance of hexamers structures in the equilibrium and the rapid time action of this equilibrium:

Therefore, in view of Brems et al., one skilled in the art would predict that a monomeric analog would remain predominantly monomeric and any association monomeric and any association observed would be to a mixture of aggregates. Thus Brems et al. suggest that the present invention would fail-the zinc-phenolic induced association of monomeric analogs into a hexamer is most unexpected. The present invention demonstrates that the claimed analogs form a well ordered, zinc/phenol hexamer ... Most significantly, the association of the monomeric analog into a hexamer does not change the time action.

*Id.* at A-375.

FN34. *See id.* at A-370 ("The addition of zinc ... does not induce aggregation to well, defined *hexamers* of the analog"-the plural of hexamers indicates that these are the structures in the equilibrium); *id.* ("the present invention claims the *hexamer* analog *complex*, formulations, and methods"-distinguishes the

molecular structure from the equilibrium.); *id.* at A-372 ("Clearly, Wollmer et al. do not disclose an *analog* containing 2 Zn ions and at least 3 phenol derivative in a *hexamer* conformation."-This sentence defines "complex" as a structure by referring to the number of molecules in the complex, and defines "hexamer" as a structure by referring to its conformation.); *id.* at A-373 ("the present monomeric analogs *complexes* and formulations"-distinguishes the structure from the equilibrium.); *id.* at A-374 ("Wollmer et al. study ... *structural* transformations of insulin *hexamers* ... [and] the 2 Zn to 4 Zn transition of insulin is a property of *hexamers*"-refers to structures); *id.* ("Wollmer et al. do not disclose des(B26-B30)-insulin in a *hexamer* conformation"-refers to the structure); *id.* ("because the CD-spectral effects observed with des(B26-30)-insulin are different and opposite than those observed with insulin *hexamers*, one of ordinary skill in the art would conclude that the *hexameric complex* could not be formed with the monomeric insulin analog."-In this section, Lilly is referring to the structure of the hexamers.).

Moreover, the following passage illustrates how Lilly attempted to distinguish the structure of the claimed hexamer complex from prior art hexamer complex:

Insulin in the presence of zinc is in a T<sub>6</sub> hexamer association state. When phenol is added, the conformation changes to a R<sub>6</sub> hexamer association. Brems et al. report that monomeric analogs do not form a hexameric T<sub>6</sub> association state with zinc. In view of Brems et al., it logically follows that one of ordinary skill in the art would predict that the monomeric analog would not change its conformation to an R<sub>6</sub>-like hexameric association state with zinc and phenol ... The present invention demonstrates that the claimed analogs form a well ordered, zinc/phenol hexamer. However, this association state is not analogous to the R<sub>6</sub> association state observed with insulin.

*Id.* at A-375.

FN35. *See id.* at A-370 ("the present invention claims the hexamer analog complex, formulations, and methods"-distinguishes the equilibrium from the molecular structures.); *id.* at A-373, A-375 ("The novelty of the present invention lies in the zinc-phenolic induced association and the subsequent rapid time action of the *formulation*"-refers to the rapid time action of the equilibrium.); Office Action of Jan. 27, 1995, Novo Ex. D at A-353 ("*formulations* are disclosed which ... are intended to provide rapid onset of action combined with improved stability."-Lilly did not dispute this use of the term "formulation" by the Examiner).

#### 4. Extrinsic Evidence

Both parties invite the Court to examine reams of extrinsic evidence, including dictionary definitions, prior art, expert testimony, and inventor testimony. Because the definitions of "complex," "hexamer," and "formulation" are clear from the intrinsic evidence of the patent, it is not necessary, and indeed improper, to examine the extrinsic evidence proffered by the parties. *See Pitney Bowes*, 182 F.3d at 1309. Therefore, the Court declines the invitation to examine the extrinsic evidence.

However, in the interests of judicial caution, in light of recent Federal Circuit law, the Court notes that the dictionary definitions are in accord with the Court's definitions.FN36 First, the dictionaries validate that "complex" means a molecular structure.FN37 The dictionary definitions do not illuminate the meaning of the term "hexamer." FN38 The parties submitted no dictionary definitions of "formulation." Therefore, the dictionary definitions do not contradict the Court's definitions of "complex," "hexamer," and "formulation."

FN36. Prevailing Federal Circuit law has always held that dictionaries are extrinsic evidence. *See, e.g.*, Vitronics, 90 F.3d at 1584-85. However, in a recent non-precedential decision, a diminished panel of the Federal Circuit held that "[d]ictionary definitions are considered to be intrinsic evidence." *Antonious v. Spalding & Evenflo Cos., Inc.*, 1999 WL 777450,\*3 (Fed.Cir.1999). Moreover, in several other cases, the court seems to have employed a dictionary as part of its intrinsic analysis of the plain meaning of the claim language. *See, e.g.*, Karlin Tech., Inc. v. Surgical Dynamics, Inc., 177 F.3d 968, 971 (Fed.Cir.1999) (using dictionary definitions as part of the intrinsic evidence analysis of the claim language); *Desper Products, Inc. v. QSound Labs, Inc.*, 157 F.3d 1325, 1333 (Fed.Cir.1998) (same). Nonetheless, absent explicit precedential authority to the contrary, this Court will consider dictionaries as extrinsic evidence. Whether the dictionaries are intrinsic or extrinsic evidence does not affect the outcome of claim construction in this case.

FN37. *See Oxford Dictionary of Biochemistry & Molecular Biology* --- (2d ed.1989) ("an aggregate of two or more molecules, particularly macromolecules, held together by non-covalent forces in a definable structural relation and as a result of particular interactions"); *Grant & Hackh's Chemical Dictionary* (1987) ("ion or compound, which in solution dissociates reversibly into its component parts" or "ion or compound which is sufficiently stable to retain its identity in solution"); *Merriam-Webster's New Collegiate Dictionary* (1998) ("a chemical association of two or more species (as ions or molecules) joined usu. by weak electrostatic bonds rather than covalent bonds"); *Merriam-Webster's New Collegiate Dictionary* (1993) (1. "a whole made up of complicated or interrelated parts"-referring in general to a type of structure; 2. "a complex substance (as a coordination complex) in which the constituents are more intimately associated than in a simple mixture"); *Webster's Third New Int'l Dictionary* (1981) ("a conjunction of varied contributing or interacting factors, elements, or qualities: as a complex substance (as a coordination compound, an ion containing several atoms, or an adsorption compound-usu. distinguished from mixture"); *Random House Dictionary* (1987) (Lilly Ex. 26) ("10. a compound in which independently existing molecules or ions of a non-metal form coordinate bonds with a metal atom or ion; 11. an entity composed of molecules in which the constituents maintain much of their chemical identity: receptor-hormone complex, enzyme substrate complex").

FN38. Only the roots of the word "hexamer" actually appear in the dictionary. *See Webster's New Collegiate Dictionary* (1989) ("hexa-" = "six; containing six atoms, groups, or equivalents"; "mer" = "member of a specified class (mono *mer*)"); *Random House Dictionary* (1987) (Lilly Ex. 26) ("hexa-" = "a combining form meaning six"; "-mer" = "a combining form meaning member of a particular group").

## **B. "pharmaceutical"**

Lilly maintains "pharmaceutical" does not have a separate meaning outside the context of "pharmaceutical formulation." Lilly then reasons that "pharmaceutical" means "an aqueous solution formulated to be of appropriate safety and efficacy for treatment of patients." D.I. 156 at 2. Like Lilly, Novo does not define "pharmaceutical" independently of "formulation." However, Novo urges a different definition, namely, "pharmaceutical" means "contain[ing] a medicinal drug or a biologically active agent and ... suitable for administration to an animal." D.I. 154 at 33. The Court holds "pharmaceutical" means "containing a medicinal drug" where "medicinal drug" means "a substance or preparation used in treating disease." FN39

FN39. Although the Court's definition of "pharmaceutical" is not identical to the definitions proffered by the

parties, this definition is more accurate. *See Exxon Chemical Patents*, 64 F.3d at 1556 ("the judge's task is not to decide which of the adversaries is correct. Instead the judge must independently ... declare the meaning of the claims").

The intrinsic evidence does not provide a clear definition of the term "pharmaceutical." First, the meaning of "pharmaceutical" is not immediately apparent from the text of the claims. Second, the specification does not define the term "pharmaceutical" and uses the term only once, without defining it:

Because all commercial *pharmaceutical* formulations of insulin contain insulin in the self-associated state and predominately in the zinc-hexamer form, it is believed that the rate-limiting step for the absorption of insulin from the subcutaneous injection depot to the bloodstream is the dissociation of the self-aggregated insulin hexamer.

'978 Patent at 1:33-39. This discussion sheds no light on the meaning of "pharmaceutical." Finally, the prosecution history provides no guidance as to the meaning of "pharmaceutical." *See Novo Ex. D.*

With the intrinsic evidence not being helpful, the Court turns to extrinsic evidence. Various dictionary definitions support the Court's definition of "pharmaceutical" as "containing a medicinal drug." FN40 Moreover, the dictionary definitions support the Court's definition of "medicinal drug" as "a substance or preparation used in treating disease." FN41

FN40. *See Oxford Dictionary of Biochemistry and Molecular Biology* 495 (1997) ("of or pertaining to drugs or pharmacy" or "any medicinal substance, mixture or formulation"); *Dictionary of Biochemistry and Molecular Biology* 355 (2d ed.1989) ("a drug" or "of, or pertaining to pharmacy" where "pharmacy" means "the branch of pharmacology that deals with the origin, the composition, the preparation, and the dispensing of drugs"); *Merriam-Webster's Collegiate Dictionary* 870 (10th ed.1998) ("of, relating to, or engaged in pharmacy" where "pharmacy" means "the art, practice, or profession, of preparing, preserving, compounding, and dispensing medical drugs"); *Merriam-Webster's New Collegiate Dictionary* 852 (1981) ("of, relating to pharmacy" where "pharmacy" means "the art or practice of preparing, preserving, compounding, and dispensing drugs"); *Grant & Hackl's Chem. Dictionary* 437 (1987) ("pertaining to drugs; the analysis of drugs and isolation of their active constituents"); *Hawley's Condensed Chem. Dictionary* 891 (1993) ("a broad term that includes not only all types of drugs and medicinal and curative products but also ancillary products such as tonics, dietary supplements, vitamins, deodorants, and the like"); *Webster's Third New Int'l Dictionary* 1694 (1981) ("of or relating to pharmacy" where "pharmacy" means "1. the administering of drugs: treatment by drugs; 2. the art or practice of preparing, preserving, compounding, and dispensing drugs").

FN41. *See Webster's Third New Int'l Dictionary* 695, 1403 ("drug" means "a substance used as a medicine" and "medicine" means "a substance or preparation used in treating disease").

The Court's definition of "pharmaceutical" comports with the idea behind the patent, to create an insulin analog formulation that is useful as a drug to treat diabetes. *See '978 Patent* at 1:11-60. Indeed, claim 10 recites a method of using a "pharmaceutical formulation" of the complex for "treating a patient suffering from diabetes mellitus." The specification defines "treating" as:

the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of a compound of present invention to prevent the onset of the symptoms or complications, alleviating the symptoms or complications, or eliminating the disease, condition, or disorder.

'978 Patent at 4:9-15. It follows that the Court's definition of "pharmaceutical" is consistent with the invention disclosed in the specification.

Lilly maintains that the term "pharmaceutical" also means that the formulation is safe and effective for treatment of diabetes. Lilly argues that "safe" means that the formulation is chemically stable and has a low rate of polymer formation. *See* D.I. 156 at 15 (citing '978 Patent at 1:57-60; 2:62; 3:5-7; 4:60-61; 5:32-34). Lilly also argues that "effective" means that the hexameric hIA retains the rapid action of monomeric hIA. *See id.* However, the specification does not state anywhere that the term "pharmaceutical" means safe and effective, as Lilly has defined the terms. Moreover, a pharmaceutical can be a medicinal drug, used in the treatment of disease, without necessarily being safe or effective. *See, e.g., In re Bendectin Litigation*, 857 F.2d 290, 321 (6th Cir.1988) (referring to the teratogenic properties of thalidomide, a medicinal drug).

Lilly also relies on the Food, Drug and Cosmetic Act definition of "drug" and criteria for "drug" approval for support of its definition. *See* 21 U.S.C. s. 321(g)(1) (1999) ("drug" means "a substance intended for use in the diagnosis, cure, mitigation, or prevention of disease"); *id.* at s. 355(b)(1)(A) (the FDA will only approve a "drug" if it is both safe and effective). However, reliance on this definition is inappropriate because the FDA, not the Patent and Trademark Office, is responsible for determining whether drugs are safe and effective and because drugs not approved by the FDA are still patentable. *See Application of Anthony*, 414 F.2d 1383, 1395 (C.C.P.A.1969).

Novo's interpretation of "pharmaceutical" is also too limiting because it includes the possibility that the formulation is "a biologically active agent" and that the formulation is "suitable for administration to an animal." A formulation containing only one hexamer complex of hIA would suffice as a "biologically active agent" but would not be "pharmaceutical" because it alone could not be used to treat a disease. Also, there is no limitation in the claims, specification, or prosecution history that a "pharmaceutical" formulation must be "suitable for administration to an animal." Instead, the touchstone is whether the formulation is "a substance or preparation used in treating disease."

For these reasons the Court declines to adopt the respective claim constructions proffered by the litigants, and instead holds that "pharmaceutical" means "containing a medicinal drug" where "medicinal drug" means "a substance or preparation used in treating disease."

### **C. "comprises ... two zinc ions"**

Lilly urges that, although "two zinc ions" means "two ions of zinc," D.I. 156 at 3, "comprises" denotes open claim language and "opens the claim to the inclusion of additional elements or materials," including more than two zinc ions per hexamer. D.I. 156 at 2, 28-29. Novo argues that "comprises" means "that the claimed human insulin analog complex can have other components in the complex, in addition to the named components in the named amounts, but can not have the named components in different amounts," D.I. 154 at 27, and that "two zinc ions" means that "each claimed complex has two and only two zinc ions." D.I. 154 at 28. Boiled down, this particular dispute centers on whether "comprises ... two zinc ions" means that each hexamer complex can have at least two zinc ions (Lilly) or only two zinc ions (Novo).

When used as a transition, as in claim 1, the term "comprises" means that the claim is open ended, so that it may include elements other than those explicitly recited in the claim. *See, e.g., Carl Zeiss Stiftung v. Renishaw*, 945 F.2d 1173, 1178 (Fed.Cir.1991). The litigants agree that the hexamer complex of claim 1 could also include calcium or acetate ions in addition to the hIA, zinc, and phenolics recited in claim 1. *See Tr.* at 241:17-23.

However, in claim 1, the use of the term "comprising" does not allow more than two zinc ions per hexamer complex because claim 1 precedes "three phenolics" with the phrase "at least" but does not precede "two zinc ions" with "at least." The expression of a limitation in one element of a claim implies the exclusion of that term in other elements of the claim. *Cf. Modine Mfg. Co. v. U.S. Int'l Trade Comm'n*, 75 F.3d 1545, 1551 (Fed.Cir.1996). Moreover, each term in each claim must be given meaning. *See Warner-Jenkinson Co.*, 520 U.S. at 29. In order to give meaning to the choice to use the term "at least" to modify only "three phenolics," claim 1 must mean that a hexamer complex can contain more than three phenolics but not more than two zinc ions per hexamer.FN42

FN42. Eli Lilly may argue that reading "comprises ... two zinc ions" to mean that there must be exactly two zinc ions renders meaningless claim 12 which is identical to claim 1 except that it uses the closed language "consisting of ... two zinc ions." However, claims 1 and 12 can be differentiated even though both are directed to the structure and not the equilibrium. Although both require exactly two zinc ions, claim 1 allows inclusion of other species in the complex, while claim 12 does not allow inclusion of any species other than the ones recited in the claim.

The Court holds that "comprising ... two zinc ions" means that the claimed human insulin analog complex may have other components in the complex, in addition to the named components, but must have the named components, including the two zinc ions, in the specified amounts.

#### **D. "consisting of"**

Lilly argues that "consisting of" indicates "closed claim language. It closes the claim to the inclusion of materials other than those recited, *except for components ordinarily associated therewith.*" D.I. 156 at 3 (emphasis added) (citing *Sakano v. Rutemiller*, 158 U.S.P.Q. 47, 51 (Bd.Pat.Interf.1968); *Ex Parte Davis*, 80 U.S.P.Q. 448, 450 (Bd.App.1948)). Novo urges that "consisting of" means that "the claim is closed to additional components ... [and] the claimed complex can include *only* the named components in the named amounts." D.I. 154 at 35 (citing *Schering v. Amgen Inc.*, 18 F.Supp.2d 372, 382 (D.Del.1998)).FN43

FN43. Novo also cites *PPG Industries v. Guardian Industres*, 156 F.3d 1351 (Fed.Cir.1998). However, that case construes the meaning of "consisting essentially of," not "consisting of" and, therefore, is not applicable.

Both parties are partially correct. *Sakano* and *Davis*, both chemical cases, hold that "consisting of" closes the claim "except for *impurities* ordinarily associated therewith." *See Sakano*, 158 U.S.P.Q. at 51; *Davis*, 80 U.S.P.Q. at 450 (emphasis added). Therefore, in the context of chemical patents, "consisting of" indicates closed claim language and closes the claim to the inclusion of unrecited elements, except for impurities ordinarily associated therewith.

**E. "wherein the human insulin analog is ... des (B27)-human insulin" and "the T<sub>6</sub> limitation"; and "hexamer" and "the R<sub>6</sub> limitation"**

Novo argues that the language "wherein the human insulin analog is ... des(B27)-human insulin" includes a limitation that the listed hIA's do not form T<sub>6</sub> hexamer structures in the presence of zinc alone ("the T<sub>6</sub> limitation"). Novo also asserts that the term "hexamer" includes a limitation that the Zn-phenolic-hIA hexamer has a conformation different from the R<sub>6</sub> conformation of the Zn-phenolic-hI hexamer ("the R<sub>6</sub> limitation").

**1. "wherein the human insulin analog is ... des (B27)-human insulin" and "the T<sub>6</sub> limitation"**

Lilly argues that "wherein the human insulin analog is ..." means that "the human insulin analog is one of the twelve recited analogs." D.I. 156 at 3. Novo argues that "wherein the human insulin analog is ..." means that "the analog in the hexamer complex *does not form a hexameric T<sub>6</sub>-like association state with zinc* and is one of the twelve analogs spelled out in the claim." FN44 D.I. 154 at 32. At bottom, the litigant's disagreement centers on whether this claim language includes a limitation that the twelve hIA's do not form a T<sub>6</sub>-like association state with zinc alone ("the T<sub>6</sub> limitation"). FN45 The Court agrees with Lilly and holds that this language does not include the T<sub>6</sub> limitation, but merely recites the twelve different types of insulin analogs that can form a hexamer complex.

FN44. Both parties agree that the twelve recited analogs in the claim are:

Asp<sup>B28</sup> human insulin

Lys<sup>B28</sup> human insulin

Leu<sup>B28</sup> human insulin

Val<sup>B28</sup> human insulin

Ala<sup>B28</sup> human insulin

Asp<sup>B28</sup> Pro<sup>B29</sup> human insulin



Lys<sup>B28</sup> Pro<sup>B29</sup> human insulin

Leu<sup>B28</sup> Pro<sup>B29</sup> human insulin

Val<sup>B28</sup> Pro<sup>B29</sup> human insulin

Ala<sup>B28</sup> Pro<sup>B29</sup> human insulin

des(B28-B30) human insulin

des(B27) human insulin.

FN45. Prior art teaches that hIA's generally do not form a stable T<sub>6</sub> hexamer complex with zinc alone. *See* Brems et al., *Altering the Association Properties of Insulin by Amino Acid Replacement*, 5 *Protein Engineering* 527, 529-33 (1992). The '978 patent also recognizes this fact. *See* '978 Patent at 2:13-15. However, at oral argument, Novo indicated that at least one of the analogs in the list of twelve does form stable T<sub>6</sub>-like association states in the presence of zinc alone. *See* Tr. at 366:21-367:11. Whatever the fact may be, it plays no part in resolution of the *Markman* issues before the Court because, *inter alia*, it lacks record support.

First, the claim language does not explicitly support this limitation. Indeed the claim language is extremely clear. It simply recites a list of twelve analogs which can comprise the insulin analog complex. There is no mention that these analogs do not form T<sub>6</sub> association states in the presence of zinc alone.

Further, the specification explicitly defines "human insulin analog" as "human insulin wherein:

Pro at position B28 is substituted with Asp, Lys, Leu, Val, or Ala; and Lys at position B29 is Lysine or substituted with Proline;

des(B28-B30); or

des(B27)."

'978 Patent at 3:47-55. In short, the patentee acted as his own lexicographer in defining the meaning of the claim term "human insulin analog."

Even though the claim language and the specification are clear, Novo nonetheless attempts to add this additional  $T_6$  limitation to the claim. It first searches the specification for this limitation. Novo cites language in the specification which states that "any aggregation between zinc and the insulin analog is distinct from that observed with insulin," '978 Patent at 2:7-9; that "AspPro-hI, AlaPro-hI, and LysPro-hI show little or no Zn-induced association and that Pro-insulin, Lys-insulin, Asp-insulin, and Ala-insulin demonstrate Zn-induced association, but less than Zn-insulin," '978 Patent at 2:18-23; and, that "insulin analogs do not form the Zn(II)- $T_6$  conformation in a manner analogous to insulin," '978 Patent at 2:29-30.

Novo ignores the principle that "interpreting what is meant by a word in a claim is not to be confused with adding an extraneous limitation appearing in the specification, which is improper." *Intervet Am., Inc. v. Kee-vet Laboratories, Inc.*, 887 F.2d 1050, 1053 (Fed.Cir.1989). In this case, Novo is attempting to import extraneous language discussing the prior art into the claim language. Since the patentee has acted as his own lexicographer in clearly defining this language, the importation of the  $T_6$  limitation is improper.

Novo further relies on the prosecution history for support of its proposed  $T_6$  limitation. This claim language was added in an amendment in response to an Office Action rejecting the claims based on a lack of enabling disclosure under 35 U.S.C. s. 112 (first paragraph) and based on prior art under 35 U.S.C. s.s. 102(b), 103(a). Novo argues that the added language requires that the twelve hIA's "not form a hexameric  $T_6$ -like association state with zinc" because of the attorney comments related to the s. 103(a) rejection:

Insulin in the presence of zinc is in a  $T_6$  hexamer association state ... Brems et al. report that monomeric analogs do not form a hexameric  $T_6$  association state with zinc. In view of Brems et al., it logically follows that one of ordinary skill in the art would predict that the monomeric analog would not change its conformation to an  $R_6$ -like hexameric association state with zinc and phenol.

Plaintiffs Ex. D, A-375.

The prosecution history can only be used to understand the meaning of the terms in the claims, not to "enlarge, diminish or vary the limitations in the claims." *Armament Systems and Procedures, Inc. v. Monadnock Lifetime Products, Inc.*, 168 F.3d 1319, 1998 WL 537746 at \*3 (Fed.Cir.1998). Novo is attempting to import a discussion of the prior art in the prosecution history into the clearly defined terms in the claims.FN46 This is not permissible. It follows this claim language does not include the  $T_6$  limitation.

FN46. "Use of the prosecution history to *interpret* claim language is distinct from prosecution history *estoppel*, which is a limitation on the doctrine of equivalents." *Chisum on Patents* at s. 18.03[d][2]; *see also* *Amhil Enterprises*, 81 F.3d at 1559. Accordingly, the Court does not reach the question of prosecution history estoppel.

Accordingly, "wherein the human insulin analog is ... des (B27)-human insulin" means that "the human insulin analog is one of the twelve recited analogs" and does not include the  $R_6$  limitation.

## 2. "hexamer" and "the R<sub>6</sub> limitation"

Novo argues that the term "hexamer" includes a limitation that the hexamer structure "is not analogous to the R<sub>6</sub> hexamer of human insulin" ("the R<sub>6</sub> limitation"). D.I. 154 at 28. Lilly answers that the term "hexamer" contains no such limitation. D.I. 156 at 2. The Court holds that the definition of "hexamer" does not include the R<sub>6</sub> limitation.

As discussed in Part IV.A, *supra*, the plain language of the claim does not include the R<sub>6</sub> limitation. The specification also includes no such limitation. Novo argues that the limitation is found in the prosecution history in attorney comments related to the s. 103(a) rejection:

In view of Brems et al., it logically follows that one of ordinary skill in the art would predict that the monomeric analog would not change its conformation to an R<sub>6</sub>-like hexameric association state with zinc and phenol ... The present invention demonstrates that the claimed analogs form a well ordered, zinc/phenol hexamer. However, this association state is not analogous to the R<sub>6</sub> association state observed with insulin.

Plaintiffs Ex. D, A-375. Novo argues that "hexamer" must refer to a structure not analogous to the R<sub>6</sub> association state because the patentee explicitly disclaimed this structure as part of the invention in order to persuade the Examiner that the invention was not an obvious improvement over the prior art.

Novo's argument fails because, as discussed in Part IV.A, *supra*, the claim language and the specification define the term "hexamer" and do not include any R<sub>6</sub> limitation. As previously rehearsed, the prosecution history can only be used to understand the meaning of the terms in the claims, not to "enlarge, diminish or vary the limitations in the claims." *Armament Systems and Procedures, Inc. v. Monadnock Lifetime Products, Inc.*, 168 F.3d 1319, 1998 WL 537746 at \*3 (Fed.Cir.1998). Like its efforts with respect to the T<sub>6</sub> limitation, Novo is attempting to import a discussion of the prior art in the prosecution history into the clearly defined terms in the claims.FN47 The R<sub>6</sub> limitation similarly fails. It is held this claim language does not include the R<sub>6</sub> limitation.

FN47. *See* n. 46, *supra*.

## F. "parenteral," "administering," and "patient"

Lilly urges that "parenteral" means "for subcutaneous injection into a patient." D.I. 156 at 3. Novo counters that "parenteral" means "taken into the body or administered in a manner other than through the digestive tract ( *e.g.*, not by mouth or through the alimentary canal)." D.I. 154 at 33. The court holds that Novo's interpretation of "parenteral" is correct.

Lilly maintains that "administering" means "subcutaneous injection." D.I. 156 at 2. Novo argues that "administer" means "to apply as a remedy." D.I. 154 at 34. The court holds that Novo's interpretation of this term is correct.

Lilly argues that "patient" means "a human being." D.I. 156 at 2. Novo replies that "patient" means "an animal, including a human being." D.I. 154 at 34. This Court holds that "patient" means an animal,

including a human being, awaiting or under medical treatment.

The meanings of "parenteral," "administering," and "patient" are not immediately apparent from reading the plain language of the claim.FN48 Moreover, the specification and the prosecution history fail to explicitly define these terms as they have done for terms such as "isotonicity agent" and "treating." *See* '978 Patent at 4:9-20. Therefore, it is appropriate to turn to extrinsic sources of evidence.

FN48. Novo argues that the doctrine of claim differentiation precludes defining the term "administering" to mean "subcutaneous injection" and the term "parenteral" to mean "subcutaneously." D.I. 154 at 35. Because the Court concludes that neither term is limited to only subcutaneous injection, the Court need not address this argument.

The dictionary definitions uniformly support Novo's definition of "parenteral" as "taken into the body or administered in a manner other than through the digestive tract ( *e.g.*, not by mouth or through the alimentary canal)." FN49 Also, the dictionary definitions of "administer" support Novo's definition of "administer" as "to apply as a remedy." FN50 Finally, the dictionary definitions of "patient" support the definition of "patient" as "an animal, including a human being, awaiting or under medical treatment." FN51

FN49. *See* Oxford Dictionary of Biochemistry and Molecular Biology 484 (1997) ("any route other than via the gastrointestinal tract, especially by injection"); Dictionary of Biochemistry and Molecular Biology 347 (2d ed.1989) ("referring to the introduction of a substance into an animal organism by ways other than that of the digestive tract"); Merriam-Webster's New Collegiate Dictionary 844 (1981) ("introduced other than by way of the intestines"); Grant & Hackl's Chem. Dictionary 423 (1987) ( "describing a route of administration of drugs or food, other than by mouth or into the intestine"); Webster's Third New Int'l Dictionary 1641 (1981) ( "1: not intestinal: situated or occurring outside the intestine ... 2: injected or for injection subcutaneously, intramuscularly, or intravenously").

FN50. *See* Merriam-Webster's Collegiate Dictionary 57 (10th ed.1998) ( "to give as a remedy"); Webster's Third New Int'l Dictionary 27 (1981) ("to give remedially (as medicine)"). There is no limitation in these dictionary definitions that administer be limited to only subcutaneous injection.

FN51. *See* Merriam-Webster's Collegiate Dictionary 863, 825 (10th ed.1998) ("patient" means "an individual awaiting or under medical care or treatment" and "individual" means "a particular being ... as distinguished from a class"); Merriam-Webster's New Collegiate Dictionary 833 (1981) ( "patient" means "an individual awaiting or under medical care or treatment"); Webster's Third New Int'l Dictionary 1152, 1655 (1981) ( "patient" means "a sick individual" or "a client for medical services" and "individual" means "a particular being or thing as distinguished from a class"). These definitions are in no way limited to only human, and not animal, patients.

Other extrinsic evidence further supports the Court's definitions of these three terms. Regarding "parenteral" and "administer," both parties agree that, at the time of the invention, it was known in the art to administer insulin to diabetics intravenously. *See* Tr. at 422:5-424:22. In addition, Lilly's expert, Dr. Michael Weiss, testified that scientists have researched nasal and pulmonary administration of insulin to diabetics. *See id.* at

105:4-11. At the time the patent claims were written, one of ordinary skill in the art would have anticipated the use of the formulation by routes other than subcutaneous injection. It follows the terms "parenteral" and "administer" are not limited to subcutaneous injection.

Regarding the term "patient," extrinsic evidence supplied by both parties supports the Court's definition by showing that animals suffer from diabetes mellitus and are treated with injections of insulin. *See* Tr. at 65:17-66:11 98:21-101:7 (testimony of Lilly expert Dr. Weiss); 219:3-15 (testimony of Novo expert Dr. Dunn). Therefore, at the time of the invention, one of ordinary skill in the art could have anticipated that an insulin analog formulation would be administered to animals, as well as human patients.

As to all three terms, Lilly urges that the disclosure of preferred embodiments in the specification limits the definition of the terms. First, Lilly takes the position that "parenteral" is limited to subcutaneous injections because the specification only discloses formulations that have rapid action when injected subcutaneously.FN52 Second, Lilly argues that the specification infers "administer" is limited to subcutaneous injections because the specification only discloses formulations that have rapid action when injected subcutaneously.FN53 Finally, Lilly insists that "patient" is limited to humans because the specification only discloses using rapid acting human insulin analogs for human patients.FN54

FN52. *See* D.I. 173 at 26 (citing '978 patent at 1:15-18; 1:28-31; 1:34-38). At the *Markman* hearing, Lilly further argued that "parenteral" must mean "subcutaneous" because the rapid action of the patented invention is only needed for subcutaneous injection of the insulin analog. *See* Tr. at 420:5-20.

FN53. *See* D.I. 173 at 26 (citing '978 patent at 1:15-18; 1:28-31; 1:34-38).

FN54. *See* D.I. 173 at 25 (citing '978 Patent at 5:21; 1:23-25).

However, the claims of the patent cannot be limited by disclosure of a preferred embodiment in the specification. *See Rhine v. Casio, Inc.*, 183 F.3d 1342, 1346 (Fed.Cir.1999). The subcutaneous method of using the insulin analog formulations and the use on humans are only preferred embodiments disclosed in the specification. As to "parenteral" and "administer," if Lilly had desired to limit the claims to only "subcutaneous" injection, it could have done so by defining these terms to mean "subcutaneous injection" or by using the term "subcutaneous" in the claims. Likewise, if Lilly had desired to limit the claims to "human patients," it could have used that language instead of "patient." Since Lilly chose to use the broader terms "parenteral," "administer," and "patient," the scope of the claims should reflect its choice of words.

The Court holds "parenteral," "administer," and "patient" have the definitions discussed above.

## **V. Conclusion**

In summary, the Court construes the disputed claim language as follows:

1. "human insulin analog complex" or "complex" (claims 1, 12) means an individual molecular structure, defined as "a chemical association state of two or more molecules held together by non-covalent bonds."

2. In claims 1 and 12, "hexamer" refers to the Zn-hIA structure, i.e., "a type of complex where six molecules of human insulin analog are held together in a single structure." In claim 13, "LysPro-human insulin is a hexamer" is shorthand meaning "in the equilibrium, most of the LysPro-human insulin molecules are in Zn-hIA structures."
3. "formulation" (claims 2-11, 13) means "an equilibrium containing molecules and molecular structures."
4. "pharmaceutical" (claims 2-11, 13) means "containing a medicinal drug" where "medicinal drug" means "a substance or preparation used in treating disease."
5. "comprises" and "two zinc ions" (claim 1) means that the claimed human insulin analog complex can have other components in the complex, in addition to the named components, but the named components, including the two zinc ions, must be in the specified amounts.
6. "consisting of" and "two zinc ions" (claim 12) indicates closed claim language and closes the claim to the inclusion of unrecited elements, except for impurities ordinarily associated therewith.
7. "wherein the human insulin analog is human insulin wherein Pro at position B28 is substituted with Asp, Lys, Leu, Val, or Ala, and Lys at position B29 is Lys or Pro; des(B28-B30)-human insulin; or des (B27)-human insulin" does not include a T<sub>6</sub> limitation;
8. "hexamer" (claims 1, 12, 13) does not include the R<sub>6</sub> limitation;
9. "parenteral" (claims 2-11, 13) means "taken or administered into the body by a means other than through the digestive tract."
10. "administering" (claim 10) means "to apply as a remedy."
11. "patient" (claim 10) means "an animal, including a human being, awaiting or under medical treatment."

TABULAR OR GRAPHIC MATERIAL SET AT THIS POINT IS NOT DISPLAYABLE PHOTO  
D.Del.,1999.

Novo Nordisk v. Eli Lilly and Co.

Produced by Sans Paper, LLC.