The "Anti" – Written Description Requirement?

Antibodies, Example 16, The Guidelines, and *Noelle v. Lederman*

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I. Introduction.

At least twenty antibody products have been introduced in the United States since 1986 for various therapeutic uses, including transplant rejection, anti-thrombosis, and various cancers and inflammatory diseases.[2] Combined sales for therapeutic antibodies are forecast to exceed $6 billion in 2005, and if merely 10% of the antibody drugs currently in clinical trials prove successful, total sales could reach $45 billion by 2009.[3] Monoclonal antibodies represent the strongest growth area in the therapeutic proteins market sector, expected to account for 48% of all sales of therapeutic proteins by 2009.[4] As the unrefined information made available by genome efforts in the 1980s and 1990s is further elaborated by proteomic, pharmacogenomic, and biological studies over the coming decades, additional validated disease targets suitable for intervention using antibodies are becoming available, and the number and therapeutic importance of

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[2] OrthoClone OKT3® (Johnson & Johnson); Panorex® (Centocor/Glaxo); ReoPro® (Centocor/Eli Lilly and Company); Antilfa® (Immunotech/SangStat); Rituxan® (IDEC/Genentech); Zenapax® (PDL/Roche); Simulect® (Novartis); Remicade® (Centocor/Schering-Plough); Synagis® (MedImmune/Abbott); Herceptin® (Genentech); Mylotarg® (Celltech/Wyeth); Campath® (ILEX/Schering AG); Zevalin® (IDEC); Humira® (Abbott/CAT); Bexxar® (Corixa/Glaxo); Raptiva® (Genentech/Serono); Xolair® (Genentech), Erbitux™ (Merck), Zevalin™ (Biogen Idec), Tysabri® (Biogen Idec).

[3] *Development and Commercialisation of Protein Therapeutics: Technologies, Pipelines and Forecasts,* Scrip Reports: PJB Publ'ns, Sept. 2004.

[4] *Id.*

antibody products will potentially further accelerate over the coming decades.[5] Thus, poised for exponential growth, the field of antibody therapeutics is veritably in its infancy.

The development of any pharmaceutical product requires an enormous investment. While it appears that the number of therapeutic antibodies will continue to grow over the next few years, whether the public receives the timely benefit of any particular antibody product may depend, among other things, on the balance that the patent laws strike between rewarding an initial invention and promoting subsequent innovation. If the patent laws reward a preliminary, narrow discovery (e.g., finding an antigen[6]) with exclusive rights over an entire field (e.g., all antibody-like chemical

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[5] In 2002, an estimated 200 distinct antibodies were being tested in clinical trials for, among other indications, transplant rejection, various cancers, various inflammatory diseases, sepsis, nephritis, myocardial infarction, infections, scleroderma, fibrosis, Alzheimer's disease, allergies, diabetes-type I, multiple sclerosis, lupus, snake/spider venom, macular degeneration, psoriasis, asthma, and arthritis. O.H. Brekke & I. Sandlie, *Therapeutic Antibodies for Human Diseases at the Dawn of the Twenty-First Century,* 2 NAT. REV. DRUG DISC. 52-61 (2003); M.A. van Dijk & J.G.J van de Winkel, *Human Antibodies as Next Generation Therapeutics,* 5 CURR. OPIN. CHEM. BIOL. 368-74 (2001). After vaccines, antibodies constitute the second most common type of biopharmaceutical agent being tested clinically, at around 20%. L.H. Stockwin & S. Holmes, *The Role of Therapeutic Antibodies in Drug Discovery,* 31 BIOCHEM. SOC. TRANS. 433-36 (2003). Finally, of a large sample of antibodies in clinical trials in 2002, PhRMA reported that about 20% were in phase III (launching ~2004 – 2008), about 33% were in phase II (launching ~2006 – 2010), and about 45% were in phase I (launching ~2008 – 2014). Pharmaceutical Research and Manufacturers of America, 2002 Survey, *371 Biotechnology Medicines in Testing Offer Hope of New Treatments for Nearly 200 Diseases available at:* http://www.phrma.org/mediaroom/press/releases/21.10.2002.600.cfm. (last visited June 20, 2005)

[6] In this paper, the word "antigen" is used to denote a molecule to which an antibody-like chemical binds. An antibody that binds to a particular antigen, such as a protein antigen, only reacts with a fraction of the whole antigen. The locus of reaction is called the antigenic determinant or the epitope. The same or similar antigenic determinant often occurs in other molecules. Therefore, an antibody that binds to a particular antigen molecule usually is also capable of binding to other molecules having different chemical structures, formula or sequence. The terms "polyreactivity" or "polyspecificity" denote binding of an antibody to molecules that are structurally unrelated, such as thyroglobulin and DNA. J.J. Marchalonis et al., *Exquisite Specificity and Peptide Epitope Recognition Promiscuity, Properties Shared by Antibodies from Sharks to Humans.* 14 J MOL RECOG. 110-21 (2001). "Epitope promiscuity" denotes the situation in which two anitgens show little or no identity in amino acid sequence but bind strongly to the same antibody as shown by either direct binding or competitive inhibition. *Id.*

materials that are later discovered to bind to that antigen), then subsequent innovation in that field may be reduced or even eliminated for the term of the patent. On the other hand, if the scope of the patent reward is commensurate with the contribution that an initial invention makes, then the "over-patenting" disincentive to subsequent innovation is removed, and more companies may be willing to undertake the enormous investment needed to discover and develop therapeutic antibody products.

It thus would seem in the public's best interest that the patent laws be applied as they historically have been, with the requirement for an adequate disclosure of an invention operating effectively to curtail the breadth of what can be patented so as to encourage others to push back the frontier of knowledge into uncharted (and unpatented) territory. The requirement of 35 U.S.C. section 112, first paragraph[7] that a patent

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See also L.C. James & D.S. Tawfik, *The Specificity of Cross-Reactivity: Promiscuous Antibody Binding Involves Specific Hydrogen Bonds Rather than Nonspecific Hydrophobic Stickiness*, 12 PROTEIN SCI. 2183–93 (2003); L.C. James et al., *Antibody Multispecificity Mediated by Conformational Diversity*, 299 SCIENCE 1362–67 (2003); L.C. James & D.S. Tawfik, *Conformational Diversity and Protein Evolution – A 60-Year-Old Hypothesis Revisited*, 28 TRENDS IN BIOCHEM. SCIS. 361-68 (2003); J.H. Arevalo et al., *Molecular Basis of Crossreactivity and the Limits of Antibody-Antigen Complementarity*, 365 NATURE 859-63 (1993); A. Kramer et al., *Molecular Basis for the Binding Promiscuity of an Anti-p24 (HIV-1) Monoclonal Antibody*, 91 CELL 799–809 (1997); J. Foote, *Immunology - Isomeric Antibodies*, 299 SCI. 1327–28 (2003); M.B.A. Oldstone, *Molecular Mimicry and Immune-Mediated Diseases*, 12 FASEB J. 1255-65 (1998); J. Inman, *The Antibody Combining Region: Speculation on the Hypothesis of General Multispecificity*, *in* THEORETICAL IMMUNOL. 243–78 (H. Bell et al., eds., 1978); N.R. Rose, *Infection, Mimics, and Autoimmune Disease*, 107 J. CLIN. INVEST., 943–44 (2001); M. Goel et al., *Plasticity Within the Antigen-Combining Site May Manifest as Molecular Mimicry in the Humoral Immune Response*, 173 J. IMMUNOL. 7358–67 (2004); J.M. Varga et al., *Mechanism of Allergic Cross-Reactions—I. Multispecific Binding of Ligands to a Mouse Monoclonal Anti-DNP IgE Antibody*, 28 MOL. IMMUNOL. 641–54 (1991).

See Guidance for Industry S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, ICH (1997), page 4, available at www.fda.gov/cder/guidance/1859fnl.pdf (last visited June 20, 2005).

For description of "binding" of antibody and antigen, *see* D.M. Webster, et al., *Antibody-Antigen Interactions*, 4 CURR. OPIN. STRUCT. BIOL. 123–29 (1994).

[7] 35 U.S.C. § 112, para. 1 (2000).

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is mostly nearly

application provide a "written description of the invention" should operate as one of the most effective U.S. patent law provisions for assuring the needed proportionality between contribution (*i.e.* what is *actually* invented) and reward (*i.e.* patent claim scope) by barring overreaching by patent applicants. It should play an essential role in promoting the timely development of innovative antibody products. It is also one of the most controversial patent law provisions.[8]

In the recent case of *Univ. of Rochester v. G.D. Searle & Co.* the United States Court of Appeals for the Federal Circuit ("Federal Circuit") affirmed a line of written description cases that, if appropriately applied, would prevent a person who merely discovers a new antigen from then validly claiming the entire field of antibodies that bind to it.[9] However, just weeks before the *Rochester* opinion another panel of the Federal Circuit issued an opinion involving the application of the written description requirement to claims for antibodies in the case of *Noelle v. Lederman.*[10] While in one aspect the panel reached a proper conclusion that one of Noelle's prior applications, whose benefit he needed to avoid a bar, failed to disclose the invention in the manner required by the first paragraph of section 112, the panel's reasoning was faulty. First, the court did not

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> connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[8] *See* Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956 (Fed. Cir. 2002), *reh'g, en banc, denied by* 63 U.S.P.Q.2d 1618 (Fed. Cir. 2002) and Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997), *cert. denied,* 523 U.S. 1089 (1998). *See also* Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916 (Fed. Cir. 2004), *reh'g denied, reh'g, en banc, denied* 375 F.3d 1303 (Fed. Cir. 2004) (Rader, J., dissenting) ("Indeed a brief survey of the literature on this topic, an astounding amount in a few short years, shows 31 articles criticizing the Eli Lilly doctrine, 7 articles defending the doctrine, and 16 neutrally commenting on the state of this evolving case law.") 375 F.3d at 1307.

[9] 358 F.3d 916. *See also Enzo*, 323 F.3d at 956; *Lilly*, 119 F.3d at 1559; Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993); Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991).

[10] 355 F.3d 1343, 1349 (Fed. Cir. 2004).

evaluate whether the claimed invention was disclosed in a prior application in the manner provided by the first paragraph of section 112, but rather whether an unclaimed and chemically unrelated substance was so disclosed. Second, the panel needlessly and wrongly declared that text from *Enzo* that cannot even be considered dicta was precedent.[11] The text in question referred to Example 16 of the Synopsis of Application of the Written Description Guidelines.[12] The *Noelle* court's unnecessary rule, like Example 16, posits that if a patent specification describes a fully characterized, novel, and unobvious antigen, then it complies with the written description requirement for a claim to any and all antibodies capable of binding to the antigen.[13] No description of any embodiments falling within the claim would be required.

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[11] *Id.*

[12] *Synopsis of Application of Written Description Guidelines* at 59-60 *available at* http://www.uspto.gov/web/menu/written.pdf (last visited June 20, 2005) [hereinafter *Training Materials*]. The Training Materials are separate and distinct from the *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1, 'Written Description' Requirement* 66 Fed. Reg. 1099 (Jan. 5 2001) [hereinafter *Guidelines*]. The Guidelines are merely to be "used by USPTO personnel in their review of patent applications for compliance with the 'written description' requirement of 35 U.S.C. 112, 1. Because the Guidelines only govern internal practices, they are exempt from notice and comment rulemaking under 5 U.S.C. 553(b)(A)." 66 Fed. Reg. at 1099. Thus, the Guidelines should be given no deference by courts, as the *Enzo* court recognized. 323 F.3d at 964. The Guidelines are *available at* http://www.uspto.gov/web/offices/com/sol/notices/writdesguide.pdf (last visited June 20, 2005). For a view of the development of the Guidelines, *see* Stephen G. Kunin, *Written Description Guidelines and Utility Guidelines*, 82 J. PAT. & TRADEMARK OFF. SOC'Y 77 (2000).

The Training Materials originated as examples in the USPTO's *Request for Comments on Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 para. 1 'Written Description' Requirement."* 63 Fed. Reg. 32639-45 (1998). After receiving comments, the USPTO published *The Revised Interim Guidelines,* 65 Fed. Reg. 71427-40 (1999) – without examples. The examples, which were deleted in their entirety from the Guidelines, became the Training Materials. In the Guidelines, the USPTO stated that "[t]he comments received with respect to the training materials will be taken under advisement as the Office revises the training materials in view of the revisions to the Guidelines." 66 Fed. Reg. at 1104. There has yet to be any reconsideration of or request for comments about the Training Materials. The USPTO also stated that "the USPTO must follow *Eli Lilly*." *Id.* at 1100. Yet, the Training Materials, particularly Examples 9, 14, 15 and 16, clearly do not follow *Lilly*. Thus, the examples in the Training Materials merit even less persuasive influence with courts than the Guidelines.

[13] 355 F.3d at 1349.

The USPTO is issuing antibody claims where the disclosure is essentially that of Example 16.[14] Furthermore, the USPTO, the European Patent Office, and the Japan Patent Office, despite eschewing reach-through claims,[15] are in substantial agreement that granting completely functionally-based claims to antibodies based on disclosure of a patentable antigen complies with their respective patent laws.[16] Finally, litigants and courts are misusing *Enzo*'s superfluous language to justify antibody claims that are in effect functionally limited and that may be quite broad.[17]

This Article addresses four questions:

1. Does Example 16 comply with the Guidelines?[18]

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[14] In a quick search, the authors found many recently-issued U.S. patents with broad antibodies claims based on disclosures similar to that summarized in Example 16, such as U.S. Patent Nos. 6,831,152, 6,849,413, 6,846,651, 6,861,226, and 6,861,227.

[15] Trilateral Project B3b, Mutual Understanding in Search and Examination, Report on Comparative Study on Biotechnology Related Patents, Theme: Comparative Study on "Reach-Through Claims," San Francisco, Cal. Nov. 5 – 9, 2001, *available at* http://www.uspto.gov/web/tws/B3b_reachthrough.pdf (last visited June 20, 2005) *See also*, S.G. Kunin, et al., *Reach-Through Claims in the Age of Biotechnology* 51 AM. U. LAW REV. 609 (2002); http://www.ipria.org/publications/workingpapers/IPRIA%2003.05.pdf (last visited June 20, 2005); and http://www.sdipla.org/events/past/grassler/ReachThru.htm (last visited June 20, 2005).

[16] Trilateral Project 24.1, Biotechnology Comparative Study on Biotechnology Patent Practices Comparative Study Report of the USPTO, the European Patent Office, and the Japan Patent Office, *available at* http://www.uspto.gov/web/tws/sr-3-bio.htm (last visited June 20, 2005). For example, the European Patent Office granted EP428602 "Claim 16. An antibody capable of binding specifically to a protein or peptide as claimed in any one of claims 1 to 4"; EP584229 "Claim 27. An antibody immunoreactive with the protein part of an L-selectin ligand polypeptide according to claim 19"; EP745124 "Claim 11. An antibody specifically binding a polypeptide encoded by a DNA sequence of Claim 1"; EP764204 "Claim 11. An antibody against the polypeptide of claim 10"; EP832233 "Claim 11. An antibody against the polypeptide of claim 10"; and EP859787 "Claim 14. An antibody against the polypeptide of claim 12." The European Patent Office, like the other offices, cannot examine such a broad claim on the basis of novelty or obviousness because the functional limitation prohibits such searching.

[17] For example, the district court in *Chiron Corp. v. Genentech Inc.*, No. 2:00-cv-01252-WBS-GGH, paper #827 (E.D. Cal. 2002), stated: "The Federal Circuit has found that a genus of monoclonal antibodies is adequately described if the antigen to which the antibodies bind is well-characterized [citing *Enzo*]."

[18] The fact that we analyze Example 16 for compliance with the Guidelines does not necessarily indicate that we agree that the Guidelines comply with the patent law.

2. Does Example 16 comply with the written description law prior to *Noelle*?

3. Was it necessary for the *Noelle* panel to say that it adopted as precedent a mere passing statement from *Enzo* involving Example 16?

4. Is the rule that the *Noelle* panel said it adopted now binding precedent on the USPTO, district courts, or on other Federal Circuit panels, and if so, what are the implications?

The authors conclude that Example 16 does not comply with the Guidelines or with the written description law prior to *Noelle*. The apparent adoption of the rule in Example 16 by the *Noelle* panel was unnecessary to decide the issue in *Noelle*, and in fact was not applied to decide the issue in *Noelle*. Therefore, the *Noelle* panel's purported rule is dicta, at best, which is not binding precedent and should not be persuasive authority for the USPTO, district courts or other panels of the Federal Circuit.

II. Example 16.

Provided below is the text of Example 16 as it appears at the USPTO's web site[19], together with explanatory footnotes to inform the reader about terminology and concepts relating to antibody structure and function.

> **Specification:** The specification teaches that antigen X has been isolated and is useful for detection of HIV infections. The specification teaches antigen X as purified by gel filtration and provides characterization of the antigen as having a molecular weight of 55 kD. The specification also provides a clear protocol by which antigen X was isolated. The specification contemplates but does not teach in an example antibodies which specifically bind to antigen

[19] *See Training Materials*, *supra* note 11, at 59-60.

> X and asserts that these antibodies can be used in immunoassays to detect HIV. The general knowledge in the art is such that antibodies are structurally well characterized.[20] It is well known that all mammals produce antibodies and they exist in five isotypes, IgM, IgG, IgD, IgA, and IgE.[21] Antibodies contain an effector portion which is the constant region and a variable region that contains the antigen binding sites in the form of complementarity determining regions and the framework

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[20] *See* GOLDSBY ET AL., IMMUNOLOGY, 76-134 (5th ed. 2003); MOLECULAR CELL BIOLOGY 1003-48 (James Darnell *et al.* eds., 2d ed. 1990); and ALBERT L. LEHNINGER, BIOCHEMISTRY 1000-07 (2d ed. 1975). Antibodies are proteins. Proteins are polymers of amino acids. Natural proteins are polymers whose monomers are the twenty naturally-occurring α-amino acids connected by amide bonds. Structure for antibodies, like all proteins, can be considered at four levels, designated as primary, secondary, tertiary, and quaternary, which differ in terms of complexity, size, and function. The sequence of amino acids in a protein's chain constitutes the primary structure. This is a linear, or one-dimensional level of structure. All of an antibody's other levels of structure and all of its functions depend upon and derive from its primary sequence. Antibodies typically are comprised of two types of amino acid chains, one called a "heavy chain" and the other a "light chain." These chains differ in amino acid sequences. The heavy chain in a full length antibody is about twice as long as a light chain.

Recognizable three-dimensional structures consisting of relatively short strings of amino acids within amino acid chains, such as the well-known α-helix and β-pleated sheet, are secondary structures. Antibodies all have these common secondary structural features.

Tertiary structure refers to the three-dimensional folding of the primary and secondary structures to give the overall shape of a protein or of significant parts of it that have distinct functions (i.e., domains). Antibodies have well-recognized tertiary structures. For example, the heavy chain of a very common class of antibodies known as immunoglobulin G ("IgG") consists of four domains, three that are called "constant" and one that called is "variable." Each IgG light chain consists of two domains, one constant and one variable. Each domain consists of about 110 amino acids, and has a molecular weight of about 12,000 daltons.

Quaternary structure exists when a protein is made up of more than one amino acid chain. IgG, for example, consists of two heavy chains and two light chains. The IgG quaternary structure is designated: H_2L_2, where "H" represents a "heavy" chain having about 430 amino acids, and "L" represents a "light" chain, having about 215 amino acids. Thus, an IgG antibody molecule has about 1310 amino acids and a molecular weight of about 150,000 daltons.

It is generally known how the amino acids in both variable and constant regions fold into α-helices and β-pleated sheets (secondary structure), and how these arrange themselves into an "immunoglobulin fold" structure having β-pleated sheets stabilized by hydrophobic interactions and by a conserved disulfide bond (tertiary structure). Antibodies consist of two light chains and two heavy chains that are held together by inter-chain disulfide bonds (quaternary structure). *Id.* Most importantly, these well-known antibody structures are not responsible for antigen binding and cannot distinguish one antibody from another.

For review of antibody structure and function, *see* E.A. Padlan, *Anatomy of the Antibody Molecule,* 31 MOL. IMMUNOL. 169 (1994).

[21] An antibody's isotype is determined by the primary structure – i.e., the amino acid sequence – of its heavy chain "constant" region. Isotype has very little or nothing to do with binding to an antigen and cannot distinguish antibodies having the function of binding to an antigen from those that do not have that function.

regions.[22] The sequences of constant regions as well as the variable region subgroups (framework regions) from a variety of species are known and published in the art.[23] It is also well known that antibodies can be made against virtually any protein.[24]

Claim: An isolated antibody capable of binding to antigen X.

Analysis: A review of the full context of the specification indicates that antibodies which bind to antigen X are essential to the operation of the claimed invention. The level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional. This is a mature technology where the level of skill is high and advanced.

The claim is directed to any antibody which is capable of binding to antigen X.

A search of the prior art indicates that antigen X is novel and unobvious.[25]

Considering the routine art-recognized method of making antibodies to fully characterized antigens,[26] the well

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[22] GOLDSBY *supra* note 20. The primary sequence of each heavy chain and light chain variable domain is typically considered to be divided into seven subsequences, four of which are called framework regions (FR1, FR2, FR3, and FR4) and three of which are called complementarity determining regions (CDR1, CDR2, and CDR3) (CDRs are also known as hypervariable regions). Within a variable domain, the framework and CDR sequences alternate as follows: FR1 – CDR1 – FR2 – CDR2 – FR3 – CDR3 – FR4. CDRs range in length from as low as three amino acids to about 25 amino acids. CDRs are the structures that are primarily responsible for an antibody's ability to bind a particular antigen. While most of the variability in structure and antigen-binding function between antibodies is due to variability in the amino acids in CDRs, frameworks also provide some of the variability.

Of the approximately 1310 amino acids within an antibody, about 110 to about 190 lie within the CDRs. *Id.* Thus, while about 8 to 15 percent of the amino acids in an antibody are within the CDRs, a smaller percentage yet are directly responsible for the functional property of antigen binding. The number, location, and type of the amino acids within CDRs that are most directly responsible for binding are totally unpredictable.

[23] These known structures are not directly responsible for antigen binding and cannot distinguish one antibody from another. Constant regions have no role in the function of antigen binding. Thus, these structures are irrelevant in the example.

[24] While this may be true in many cases, the statement ignores the known difficulties of producing some antibodies that could constitute undue experimentation, or otherwise weigh against an assumption that the art enables across the entire scope of what may be a broad genus of antibodies. *See In re* Wands 858 F.2d 731 (Fed. Cir. 1988).

[25] This is relevant to the patentability of antigen X, not to the patentability of antibodies that bind antigen X.

> defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X.
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> **Conclusion:** The disclosure meets the requirement under 35 USC 112 first paragraph as providing an adequate written description of the claimed invention.

III. Summary of the Guidelines.

Before considering whether Example 16 complies with the Guidelines, this section summarizes the analytical approaches that the Guidelines provide for determining whether a particular description complies with 35 U.S.C. section 112, first paragraph.

"Step-by-Step" Analysis.

The Guidelines provide a step-by-step methodology for determining the adequacy of written description for original claims.[27] The steps are:

1. Determine what the claim as a whole covers.

   The Guidelines require that each claim must be given its broadest reasonable interpretation in light of and consistent with the written description.[28]

2. Review the entire specification to understand how applicant provides support for the claimed invention, including each element and/or step.

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[26] Antibodies may be made by a so-called "routine art-recognized method of making antibodies" even if an antigen is not "fully-characterized."

[27] *Guidelines*, 66 Fed. Reg. 1099, 1105-07 (Jan. 5, 2001). The step designations that are used in the Guidelines are also used herein.

[28] *Id.* at 1105.

From the standpoint of one of skill in the art at the time the application was filed, the examiner must "compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention."[29] The examiner must also determine the field of the invention and the level of skill and knowledge in the art. The specificity of disclosure needed to fulfill the written description requirement and the level of skill and knowledge in the art are inversely related. Finally, the specification need not contain a detailed description of information that is well known in the art.[30]

3. Determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention as a whole at the time the application was filed.

   a. Original Claims.

      (1) Species Claims.[31]

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[29] *Id.*

[30] *Id.*

[31] Because the claim under consideration is a genus claim and because no antibody species were described in Example 16's hypothetical specification, the Guidelines' step-by-step method and factors to be considered for species claims are included in this footnote rather than in the main text.

For each claim drawn to a single embodiment or species:

(a) Determine whether the application describes an actual reduction to practice of the claimed invention;

(b) If not, then determine whether the invention is complete as evidenced by a reduction to drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole;

(c) If not, then determine whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention;

(i) Determine whether the application as filed describes the complete structure of the claimed invention as a whole;

(2) Genus Claims.

The written description requirement for a genus may be satisfied through sufficient description of a "representative number of species" by: actual reduction to practice; reduction to drawings; or disclosure of relevant, identifying characteristics, *i.e.* structure or other physical and/or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show that the applicant was in possession of the claimed genus.[32] A genus claim in an application that fails to adequately describe a representative number of species must be rejected under 35 U.S.C. section 112, first paragraph.[33]

Level of Skill and Knowledge in the Art.

In order to determine the level of skill and knowledge in the art, the Guidelines state:

(ii) If not, then determine whether the specification discloses "other relevant identifying characteristics" sufficient to describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention.

The Guidelines provide "factors to be considered" in determining under (c)(ii) above whether a skilled artisan would recognize that the applicant was in possession of a claimed species invention. These are: the level of skill and knowledge in the art; partial structure; physical and/or chemical properties; functional characteristics alone or coupled with a known or disclosed correlation between structure and function; and the method of making the claimed invention. According to the Guidelines, disclosure of "any combination of such identifying characteristics" that distinguishes the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. 66 Fed. Reg. at 1106, (citing Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d. 1559, 1568 (Fed. Cir. 1997)).

A species claim in an application that fails to meet at least one of criteria (a), (b), or (c) above must be rejected under 35 U.S.C. section 112, first paragraph.

[32] 66 Fed. Reg. at 1106. The Guidelines provide further comments about evaluating a genus claim, which are discussed below in the section entitled "Factors to Be Considered for a Genus Claim."

[33] *Id.*

> Patents and printed publications in the art should be relied upon to determine whether an art is mature and what the level of knowledge and skill is in the art. In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention.[34]

However, the Guidelines also recognize that for some inventions, "more evidence" than mere citation of function "is required to show possession."[35]

Partial Structure.

"[D]isclosure of a partial structure without additional characterization of the product may not be sufficient to evidence possession of the claimed invention."[36]

Structure, Function, and Correlation.

With regard to correlation between structure and function, the Guidelines state that:

> [I]f the art has established a strong correlation between structure and function, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function. Thus, the written description requirement may be satisfied through disclosure of function and minimal

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[34] *Id.* (citing *In re* Hayes Microcomputer Prod., Inc. Patent Litig., 982 F.2d 1527, 1534-35 (Fed. Cir. 1992)):

> One skilled in the art would know how to program a microprocessor to perform the necessary steps described in the specification. Thus, an inventor is not required to describe every detail of his invention. An applicant's disclosure obligation varies according to the art to which the invention pertains. Disclosing a microprocessor capable of performing certain functions is sufficient to satisfy the requirement of section 112, first paragraph, when one skilled in the relevant art would understand what is intended and know how to carry it out.

[35] *Id.*

[36] *Id.* at 1106 and 1110 n.53 (citing and extensively quoting Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir. 1991)).

> structure when there is a well-established correlation between structure and function. In contrast, without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. In this latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement.[37]

Method of Making.

"[D]isclosure of only a method of making the invention and the function may not be sufficient to support a product claim other than a product-by-process claim."[38] An original claim may fail to meet the written description requirement when the invention "is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between structure and function."[39] The Guidelines state that:

> A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.[40]

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[37] *Id.* at 1106 and 1110, n.49 (emphasis added) (citing Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d. 1559, 1568 (Fed. Cir. 1997) (written description requirement not satisfied by merely providing "a result that one might achieve if one made that invention")); also citing *In re* Wilder 736 F.2d 1516, 1521 (Fed. Cir. 1984) (affirming a rejection for lack of written description because the specification does "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). *Cf.* Fonar Corp. v. Gen. Elec. Co., 107 F.3d 1543, 1549 (Fed. Cir. 1997) (disclosure of software function adequate in that art)).

[38] *Guidelines*, 66 Fed. Reg. at 1106.

[39] *Id.*

[40] *Id.* at 1108 n.14.

The written description requirement is not met for an original claim when "the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."[41]

Additional Guidance for Evaluating a Genus Claim.

The Guidelines provide that a "representative number of species" means that any species that are adequately described must be representative of the *entire* genus. [42] Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.[43] While situations may exist where adequate description of one species will support a genus claim, for inventions in an unpredictable art, adequate written description of a genus that embraces widely variant species *cannot* be achieved by disclosing only one species within the genus.[44] What constitutes a "representative number of species" is said to be "an inverse function of the skill and knowledge in the art."[45] Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed."[46]

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[41] *Id.* at 1105.

[42] *Id.* at 1106.

[43] *Id.*

[44] *Id.*

[45] *Id.*

[46] *Id.* Whatever the number of species actually described, they must lend predictability as to species within the genus that are not act actually described.

With regard to genus claims, the Guidelines finally state, "Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces."[47] An example of this principle, according to the Guidelines, is an application that discloses an amino acid sequence and claims the genus of nucleic acids that encode the amino acid sequence.[48] Since the Genetic Code is widely known, disclosure of an amino acid sequence provides sufficient information for possession of the genus of nucleic acids that encode the sequence, but not necessarily for possession of any particular species within the genus.[49]

IV. Application of the Guidelines to Example 16.

"Step-by-Step" Analysis.

1. Determine what the claim as a whole covers.

The Guidelines require that each claim must be given its broadest reasonable interpretation in light of and consistent with the written description. [50] The ordinarily skilled person would certainly conclude that a claim for "an isolated antibody capable of binding to antigen X" includes more than a single antibody. It is also reasonable to conclude that this claim includes a wide variety of chemical structures. The claim

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[47] *Id.*

[48] *Id.* at 1106 n.57.

[49] *Id.* at 1111 n.57.

[50] *Id.* at 1105. *See also In re* Hyatt, 211 F.3d 1367, 1372 (Fed. Cir. 2000) ("[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification.").

encompasses any and all isolated antibodies having any measurable binding to antigen X. Even though the specification contemplates antibodies that *specifically* bind to antigen X, the claim merely recites *"capable"* of binding to antigen X. It is reasonable to assume that *capable* is a much lower standard than *specifically*, which provides yet further basis to construe the genus claim very broadly for examination purposes.

The claim covers antibodies that bind to antigen X at any of potentially many locations on antigen X.[51] The strength of binding and location of binding are primarily influenced by the amino acid sequences of the complementarity determining regions (CDRs) and secondarily by the amino acid sequences of the frameworks.[52] The variety of CDRs and framework amino acid sequences (FRs) for antibodies that bind antigen X over a wide range of binding strengths and locations of binding is extremely diverse, with no amino acid sequences in the CDRs and FRs commonly shared by all antibodies that bind.[53]

Furthermore, the broadest reasonable interpretation includes antibodies that are discovered using classical immunization techniques, those that are derived from antibody libraries, and those that are engineered from pre-existing antibodies by changing any of a variety of amino acid modifications in the CDRs and FRs. Such deliberate engineering may affect binding location or strength, specificity, pharmacokinetics,

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[51] A location on an antigen where an antibody binds is called an epitope or an antigenic determinant. *See supra* note 6.

[52] *See* GOLDSBY *supra* note 20.

[53] Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d. 1559, 1568 (Fed. Cir. 1997). *See* P.D. Jeffrey et al., *Structure and Specificity of the Anti-Digoxin Antibody* 248 J MOL. BIOL. 344 (1995); C. Monnet et al., *Highly Specific Anti-Estradiol Antibodies: Structural Characterisation and Binding Diversity.* 315 J MOL. BIOL. 699 (2002); PCT Patent Application Int'l Publ'n No. WO 02/02641 *Antibodies That Immunospecifically Bind to BLyS* (published Jan. 10, 2002) [hereinafter WO 02/02641]; and Bryan M.

pharmacodynamics, and chemical and physical stability in solution, among other factors.[54]

The claim covers antibodies that would be used merely as analytical tools for detecting antigen X (e.g., the immunoassay that the specification mentions) and also those that would be used to purify antigen X, to detect antigen X diagnostically in an animal or *in vitro*, and to treat or prevent conditions related to antigen X in an animal.[55] In summary, the claim covers "any antibody which is capable of binding to antigen X."[56]

2. Review the entire specification to understand how applicant provides support for the claimed invention, including each element.

The specification merely states an intended function of the claimed antibodies – binding to antigen X.[57] No antibodies were actually made.[58] No antibodies were shown to bind to antigen X. The specification provides no drawings or structural chemical formulas of antibodies that bind to antigen X, nor any information about structures (e.g., CDRs and FRs) responsible for binding, and no structure-function correlation between CDR and FR amino acid structures responsible for binding and the function of binding to antigen X.

Edwards, et al., *The Remarkable Flexibility of the Human Anitbody Repertoire; Isolation of Over One Thousand Different Antibodies to a Single Protein, BlyS,* 334 J. MOL. BIOL. 103-18 (2003).

[54] WO 02/02641 *Antibodies That Immunospecifically Bind to BlyS* (Using phage display technology, thousands of distinct antibody molecules having various properties were created that bind to an antigen designated as BlyS).

[55] In view of the great structural diversity and the unpredictable and widely varying functional properties, such as affinity, specificity, neutralization, stability, pharmacokinetics, pharmacodynamics, and toxicology, the members of this vast genus would not necessarily each be useful for each of the stated uses. However, issues involving section 112 first paragraph (enablement) and section 101 (utility) are beyond the scope of this article.

[56] *Training Materials, supra* note 11, at 60.

[57] *Id.* at 59.

3. Determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention as a whole at the time the invention was filed.

A genus of antibodies is claimed. The primary inquiry under the Guidelines with respect to genus claims is whether sufficient description of a "representative number of species" is provided.[59] Since Example 16 provides *no* species, the claim must be rejected.[60] Nevertheless, to address the view that "one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed,"[61] it is instructive to continue the inquiry by asking whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Such common attributes or features still must be of the sort described by "relevant identifying characteristics" – i.e. structure, physical and/or chemical properties, or functional characteristics coupled with known or newly disclosed correlation between structure and function.[62] Where function instead of structure is relied upon, as in Example 16, there must be a "a strong correlation between structure and function" such as would allow "one skilled in the art [to] be able to predict with a reasonable degree of confidence the structure . . . from a recitation of its function" or "function and minimal structure when there is a well-established correlation between structure and function."[63]

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[58] The mere provision of one or even of many antibodies is unlikely to provide sufficient representative species to support a genus covering all antibodies that are capable of binding an antigen.

[59] *Guidelines*, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001).

[60] *Id.* The Guidelines provide no guidance for the situation, as in Example 16, in which no actual species are described.

[61] *Training Materials, supra* note 11, at 59-60.

[62] 66 Fed. Reg. at 1106.

[63] *Id.* at 1110 n.49.

The specification in Example 16 discloses that the function of the claimed antibody is "binding to antigen X." Thus, under the Guidelines possession might be shown if there were a strong correlation between structure and function such as would allow one skilled in the art to be able to predict with reasonable confidence the structure of all the claimed antibodies from recitation of the function of binding to antigen X, or if the specification disclosed a partial structure and if a well-established correlation existed that would allow the skilled person to envision the remainder of the structure responsible for the function.[64]

The structure relevant to the function of binding to antigen X cannot include the constant regions because these are conventional and not involved in antigen binding.[65] Instead, as discussed above, the relevant structure must be the variable regions, particularly the CDRs and to some extent the frameworks.[66]

Is there sufficient knowledge in the antibody art such that mere recitation of the function "binding to antigen X" would permit one skilled in the art to predict with reasonable confidence the structure(s) (primary sequence) of antibodies that the claim encompasses? In the authors' opinion, the answer is patently "No." There is no "Antibody Code" analogous to the Genetic Code to correlate antigen and antibody structures.[67] Neither can the variable regions that are responsible for binding to antigen

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[64] *Id.* at 1106.

[65] *See supra* note 22. Example 16 admits that the structures of the constant regions of all human and mouse isotypes are known. *Training Materials, supra* note 11, at 60.

[66] *See* GOLDSBY *supra* note 20.

[67] The function of a polynucleotide is "encoding" a protein. The relationship between polynucleotide structure and function is known with certainty. Given a particular polynucleotide sequence (structure, e.g., cDNA), the sequence of the protein encoded or expressed is known with certainty from the Genetic Code. Likewise, given a protein amino acid sequence, the structure of one or all of the polynucleotide

be described by simple rules of complementarity like those that apply to the hybridizing or mutual binding of complementary strands of polynucleic acids.[68] Furthermore, the specification of Example 16 does not disclose a newly recognized correlation between the structure of variable regions (i.e. their primary sequences) and the antigen binding function. Thus, there is no newly disclosed or art-recognized correlation between the structure of variable regions and the antigen binding function of the sort that would be required for Example 16 to pass muster under the written description requirement.

To summarize, very much is known about antibody structure generally and about the general relationship between certain portions of the antibody structure and particular antibody functions. However, the antibody structures responsible for the claimed function of "binding antigen X" are precisely the structures that are not known, that are not newly disclosed, and that cannot be predicted from a structure-function correlation. Therefore, the specification in Example 16 fails to disclose "other relevant identifying characteristics sufficient to describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention."[69] Example 16 fails to meet any of the criteria in the Guidelines' step-by-step analysis for a genus claim, and accordingly must be rejected.[70]

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structures that encode that sequence is known with certainty from the Genetic Code. An "Antibody Code" analogous to the Genetic Code would permit one, in principle, to either describe all the antibody variable region structures that would bind to an antigen X, or to determine (without laboratory tests) whether any particular antibody variable region structure would bind to antigen X.

[68] *See* Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956 (Fed. Cir. 2002).

[69] 66 Fed. Reg. at 1106.

[70] This conclusion is consistent with the circumstances in which the Guidelines recognize the potential to fail to meet the requirement, *i.e.* "if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." 66 Fed. Reg. at 1105. This problem may arise when an invention is described solely by its function and process for making it, and: 1) there is no described or art-recognized

Such a conclusion is completely consistent with case law, which prohibits a genus claim when the specification does not define any structural features that are both necessary for achieving the function and commonly possessed by all members of the genus, and when there is no known or disclosed correlation between the function and the structure(s) required to achieve it.[71] Because the genus claim of Example 16 is fundamentally defined solely by what it does rather than what it is, there is no indication of possession of the genus.[72] One skilled in the art cannot visualize or recognize the identity of the members of the genus.[73]

V. How Did the USPTO Reach the Wrong Conclusion in Example 16?

The authors are not aware of the process the USPTO followed in drafting Example 16, or of what technical facts and legal precedents were considered. To us, as patent practitioners who are very familiar with patent law and the technology of antibodies, the example seems to be disconnected from common knowledge of antibody structure and function, and also to lack legal justification. It appears that the drafters analyzed the claim as a species claim covering a single embodiment even though acknowledging that a "spectrum" of antibodies would have the functional property of

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correlation or relationship between structure and function; or 2) the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the process. *Id.* As discussed above, there is no described or art-recognized correlation or relationship between antibody structure (amino acid sequence) and the function of binding to antigen X. Furthermore, the knowledge and level of skill in the antibody art is not such as to permit a skilled person to immediately envisage any antibody that binds to antigen X. Thus, Example 16 should have failed to meet written description requirement under the second of the "two instances."

[71] *Id.*

[72] *Id.*

[73] For this reason, functional claims in general, and functionally-limited antibody claims in particular can only be examined for novelty or obviousness with great difficulty, if at all.

binding to antigen X and that the claim covered "any antibody which is capable of binding to antigen X."[74] All of the factors in Example 16 are "factors to be considered" for species claims:[75] the level of skill and knowledge in the art,[76] partial structure,[77] functional characteristics alone,[78] and a method of making the claimed invention.[79] None of the factors in Example 16 (besides skill of the art) are directly relevant to the consideration of a genus claim; they only bear on assessing whether any actually-disclosed species within the genus are each adequately described.[80]

Yet even if these "species" factors are considered, the conclusion in Example 16 is still incorrect. For example, characterization of the antibody art as "a mature technology where the level of skill is high and advanced" is a statement that is unguided

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[74] "[O]ne of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X." *Training Materials, supra* note 11, at 60. The quotation also reveals that the drafters of Example 16 created a new principle in patent law, which would permit an adequate written description of a first thing to *implicitly* provide an adequate written description of a "spectrum" of other things that bear not the slightest resemblance to the first thing.

[75] 66 Fed. Reg. at 1106. *Also, see supra* note 31.

[76] "This is a mature technology where the level of skill is high and advanced." *Training Materials, supra* note 11, at 59-60.

[77]

> The general knowledge in the art is such that antibodies are structurally well characterized. It is well known that all mammals produce antibodies and they exist in five isotypes, IgM, IgG, IgD, IgA, and IgE. Antibodies contain an effector portion which is the constant region and a variable region that contains the antigen binding sites in the form of complementarity determining regions and the framework regions. The sequences of constant regions as well as the variable region subgroups (framework regions) from a variety of species are known and published in the art.

Id. Cf. "the well defined structural characteristics for the five classes of antibody . . . ." *Id.*

[78] "the functional characteristics of antibody binding . . . ." *Id.*

[79] "It is also well known that antibodies can be made against virtually any protein." *Id.*

"The level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional." *Id.*

by any legal precedent or principle of which the authors are aware and is also factually indefensible. Neither case law, the Guidelines, nor the USPTO's Manual of Patent Examining Procedure define the term "mature" in this context or provide guidance for determining whether a technology is mature.[81] Furthermore, as discussed at length above, the knowledge and level of skill in the antibody art is not so high and advanced as to permit a skilled person to immediately envisage the structures of the claimed antibodies from simply stating that the intended function is to bind to antigen X.

With regard to disclosure of function and a method of making, the Guidelines instruct that these may suffice in mature arts in which the level of knowledge and skill are presumptively high.[82] In the case cited by the Guidelines to justify not rejecting an original claim that recites only function, the structure at issue was a computer program for achieving certain described functions.[83] The court found that there was well-known

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[80] The genus inquiry focuses on assessing whether representative species have been adequately described, as discussed previously (*see supra* note 58), and below (*see infra* note 91).

[81] The statement in the Guidelines that "[p]atents and printed publications in the art should be relied upon to determine whether an art is mature" provides no guidance as to what must be found in the patents and publications that would warrant a conclusion that an art is "mature." 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001).

[82] *Id.*

> "In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention."

Id. at 1106. As noted above, the Guidelines provide no citation supporting or explaining the term "mature."

[83] *In re* Hayes Microcomputer Prod., Inc. Patent Litig., 766 F. Supp. 818 (N.D. Cal. 1991). The invention in this case was an improved mechanism for detecting an escape command in a modem. The improvement comprised a "timing means" and a "means, operative . . . [to carry out another function]." The infringer alleged that the specification failed to meet the written description requirement because it did not list programs for carrying out these two functions. The court concluded that no program listings were required to comply with the written description requirement, because one skilled in that art could write a program to carry out those functions.

See also, Fonar Corp. v. Gen'l Elec. Co., 107 F.3d 1543, 1549 (Fed. Cir. 1997):

correlation between structure and function, such that from mere recitation of function the structure of a program to accomplish that function could be described.[84] Hence, the right question is not whether the art has been practiced a long time or is "mature" but whether the art has developed to the point that the structure responsible for a function can be described from recitation of function.

Has the antibody art developed to this level of maturity? Example 16 suggests that it has, and this is seen in Example 16's juxtaposition of true statements about structure and function of antibodies, which invite the conclusion that the antibody art is mature and the level of knowledge and skill is high.[85] However, as discussed above, this knowledge is largely irrelevant to the function of binding a new antigen and is insufficient to provide the structure-function correlation required to permit mere

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> As a general rule, where software constitutes part of a best mode of carrying out an invention, description of such a best mode is satisfied by a disclosure of the functions of the software. This is because, normally, writing code for such software is within the skill of the art, not requiring undue experimentation, once its functions have been disclosed. Thus, flow charts or source code listings are not a requirement for adequately disclosing the functions of software.

66 Fed. Reg. at 1108 n.14.

[84] In the computer art, it is also possible to deduce function from description of structure and vice versa. The same is not possible in the antibody art.

[85]

> The general knowledge in the art is such that antibodies are structurally well characterized. It is well known that all mammals produce antibodies and they exist in five isotypes, IgM, IgG, IgD, IgA, and IgE. Antibodies contain an effector portion which is the constant region and a variable region that contains the antigen binding sites in the form of complementarity determining regions and the framework regions. The sequences of constant regions as well as the variable region subgroups (framework regions) from a variety of species are known and published in the art.

Training Materials, supra note 11, at 59-60.

recitation of function to satisfy the written description requirement.[86] Similarly, this knowledge does nothing to distinguish the claimed antibodies from other things.[87]

The Guidelines allow consideration of partial structures for species and Example 16 relies heavily on the extensive knowledge of certain general, but partial, structures of antibodies.[88] Of course, nothing is known or could be known about the structures responsible for the function of binding to antigen X, for otherwise the claim would be anticipated. Additionally, nothing about these known partial structures distinguishes the claimed antibodies from the art. Therefore, extensive knowledge about known structures in antibodies should be irrelevant to the question of compliance with the written description requirement, even for a species claim.

Finally, with regard to the role of function, the Guidelines seem to be contradictory as to whether functionality alone may be a factor to be considered. In the "other factors to be considered" for a species claim, functionality alone (without structure) is said to be a factor to be considered.[89] However, every other such reference in the Guidelines requires function to be coupled with a structure-function correlation that

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[86] 66 Fed. Reg. at 1106.

[87] The Guidelines require "distinguishing identifying characteristics" for a species claim. *Id.*

[88]

> The general knowledge in the art is such that antibodies are structurally well characterized. It is well known that all mammals produce antibodies and they exist in five isotypes, IgM, IgG, IgD, IgA, and IgE. Antibodies contain an effector portion which is the constant region and a variable region that contains the antigen binding sites in the form of complementarity determining regions and the framework regions. The sequences of constant regions as well as the variable region subgroups (framework regions) from a variety of species are known and published in the art.

Id.

[89] *Id.*

is known or disclosed.[90] Thus, Example 16 also fails in this respect for a species claim. In summary, even when merely the "species" factors are considered, Example 16 is deficient.

The Guidelines' "factors to be considered" require certain findings to be made.[91] Example 16 failed to make findings for any of these facts relevant to a genus claim,

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[90] An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Id (emphasis added, citations omitted)..

> Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

Id (emphasis added).

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice . . ., reduction to drawings . . . , or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Id (emphasis added).

[91] Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

Id. (emphasis added).

The Guidelines provide more factors to be considered in unpredictable arts, such as proteins:

> [F]or inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which

except for the level of skill with respect to making antibodies, and gave undue and unfounded weight to this factor. A proper consideration of the "factors" for a genus claim would result in the following findings of fact and conclusion:

- antibodies are chemicals;
- the chemical arts are considered unpredictable;
- this invention is characterized by factors that are not reasonably predictable;
- no representative species are provided;
- no complete or even partial structures responsible for binding to antigen X are provided;
- no physical and/or chemical properties are provided;
- only the functional characteristic of binding to antigen X is provided;
- the art, as advanced in some respects as it is, provides no teaching with respect to the specific structures responsible for binding antigen X;
- there is no known or disclosed correlation between antibody structure (variable region primary sequences) and function of binding to antigen X; and
- the level of skill and knowledge in the art is high with respect to methods of making antibodies in general.

Considering these factors, the claim of Example 16 must be rejected because the specification fails to comply with the Guidelines.

> are known to one of ordinary skill in the art, more evidence is required to show possession. For example, disclosure of only a method of making the invention and the function may not be sufficient to support a product claim other than a product-by-process claim (citing *Fiers* and *Amgen*). Furthermore, disclosure of a partial structure without additional characterization of the product may not be sufficient to evidence possession of the claimed invention (citing *Amgen*).

Id.

VI. The Written Description Requirement.

For a patent to be valid, it must comply with the first paragraph of 35 U.S.C. section 112.[92] The USPTO and the courts interpret this paragraph to contain three independent requirements: (1) a written description of the invention; (2) a disclosure of how to make and use the invention (enablement); and (3) a disclosure of the best mode of practicing the invention.[93] Failure of a patent application to satisfy any of these requirements is grounds for rejection of an application or invalidation of an issued patent. Courts have consistently emphasized the fact-sensitive nature of the written description requirement,[94] and have suggested that broadly articulated rules setting forth a standard for fulfillment of the written description requirement are inappropriate.[95] However, the policy considerations are the same regardless of the invention.[96] In order to prevent overreaching by the patentee and yet encourage innovation, it is important that the written description requirement be closely linked with what is necessary to demonstrate conception of an invention.[97] Demonstrating "possession" of an invention is evidencing the "completed conception." Thus, the cases beginning with *Amgen*, where the Federal

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92 35 U.S.C. §112, para. 1, *see supra* note 7.

93 *See* Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722 (2002); Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916 (Fed. Cir. 2004); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555 (Fed. Cir. 1991); Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir. 1991).

94 *See, e.g., Vas-Cath*, 935 F.2d at 1562; *In re* Smith, 458 F.2d 1389 (C.C.P.A. 1972) (stating that determination of compliance with § 112 is a case-by-case inquiry); *In re* DiLeone, 436 F.2d 1404 (C.C.P.A. 1971) (stating that what is necessary to fulfill the written description requirement varies depending on the nature of the invention).

95 *In re* Wertheim 541 F.2d 257, 263 (C.C.P.A. 1976). *See also In re* Driscoll 562 F.2d 1245, 1250 (C.C.P.A. 1977) (stating that the precedential value of written description cases is extremely limited).

96 Paula K. Davis & Steven P. Caltrider, *Timing (of Invention) Is Everything: The Essential Role of The Written Description Requirement*, 15 FED. CIR. B. J. (forthcoming 2005). *See also* James J. Kelley, *Are There Two or Three Requirements in 35 U.S.C. § 112, para. 1? THERE ARE THREE*, INTELL. PROP. TODAY, Jan. 2004, at 34.

97 *Id.*

Circuit discussed what is necessary to show a completed conception, and continuing with *Fiers*, *Lilly*, *Enzo*, and *Rochester*, where the court specifically addressed the written description requirement, represent a logical and consistent explanation of the law as it should be applied to inventions involving biotechnology compositions such as DNA, protein, and antibodies.[98]

In *Amgen*, the Federal Circuit held that the Amgen patent was not invalidated by prior development of a probing strategy to screen a DNA library, even though this strategy eventually resulted in the actual cloning of the gene.[99] The earlier work was insufficient to constitute a conception of the DNA encoding EPO.[100] The court noted that "[c]onception is the 'formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice.'"[101] Applying chemical case law precedent, the court stated, "Conception requires both the idea of the invention's structure and possession of an operative method of making it."[102] Further, the court held:

> Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principle biological property, e.g., encoding human erythropoietin, because an alleged conception having no more specificity than that is

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[98] Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 969 (Fed. Cir. 2002); Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1566 (Fed. Cir. 1997); Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993); *Amgen*, 927 F.2d at 1207.

[99] *Amgen*, 927 F.2d at 1206.

[100] *Id.*

[101] *Id.* (quoting Hybritech Inc. v. Monoclonal Antibodies, Inc. 802 F.2d 1367, 1376 (Fed. Cir. 1986), *cert denied*, 480 U.S. 947 (1987)).

[102] *Id.* (citing Oka v. Youssefyeh 849 F.2d 581, 583 (Fed. Cir. 1988)).

> simply a wish to know the identity of any material with that biological property.[103]

The court also noted that an inventor would be unable to envision the detailed constitution of a gene until after the gene had been cloned and characterized.

In *Fiers*, the Federal Circuit clearly set forth the relationship between conception and the written description requirement.[104] The court concluded that a statement merely referring to DNA encoding β-interferon in conjunction with a method of isolating the DNA did not indicate the applicant was in possession of the particular DNA.[105] Noting that the reasoning applied in *Amgen* regarding conception also applies to the adequacy of descriptions, the court stated that

> [S]uch a disclosure just represents a wish, or arguably a plan, for obtaining the DNA. If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity. To paraphrase the Board, one cannot describe what one has not conceived. [106]

Fiers argued that *Amgen* was distinguishable because in *Amgen* the court was dealing with a situation where the isolation of the EPO DNA was "attended by serious difficulties."[107] Fiers suggested that the standard for proving conception of a DNA is essentially the same as that for proving enablement. The court disagreed and stated "[I]rrespective of the complexity or simplicity of the method of isolation employed,

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[103] *Id.*

[104] *Fiers*, 984 F.2d at 1171.

[105] *Id.* An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. *Id.*

[106] *Id.* at 1171

[107] *Id.* at 1168.

conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility."[108] With regard to the scope of the claimed invention, the court explained that "[c]laiming all DNAs that achieve a result without defining what means will do so is not in compliance with the description requirement; it is an attempt to preempt the future before it has arrived."[109]

In *Lilly*, the Federal Circuit held that a description of the isolation of rat proinsulin messenger RNA, the synthesis and characterization of rat proinsulin complementary DNA (cDNA), a method of obtaining human cDNA for proinsulin using a prophetic example using the same method used to obtain rat proinsulin cDNA, and the amino acid sequences of human proinsulin already known in the art was not enough to adequately describe the cDNA encoding human proinsulin and other vertebrate and mammalian proinsulins.[110] Clearly distinguishing the written description and enablement requirements, the court stated,

> Whether or not it provides an enabling disclosure, it does not provide a written description of the cDNA encoding human insulin . . . . While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA.[111]

In determining whether the applicant provided an adequate written description to support a genus of vertebrate proinsulins, the court noted that every species encompassed by a genus need not be specifically described; however, a description of a single species

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[108] *Id.* at 1169.

[109] *Id.*

[110] Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1567 (Fed. Cir. 1997).

[111] *Id.*

does not always constitute a description of a genus encompassing it.[112] The court stated that:

> a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.[113]

Furthermore, and most importantly for antibody genus claims, the generic claim itself could not provide its own written description because it claimed the genus solely by function (cDNA encoding vertebrate or mammalian insulin).[114] Thus, genus claims fail written description when a specification lacks a representative number of species within the class and when the genus is defined only by what it does rather than what it is.

In *Enzo*, the Federal Circuit considered whether a patent that merely stated the intended function for the claimed invention (DNA fragments that specifically bind to the DNA of *N. gonorrhoeae*) without any disclosure of the structures responsible for such function satisfied the requirement for a written description of the invention.[115] The court concluded that a functional property, such as, binding specificity, is insufficient for a genus of DNA fragments.[116] The court stated:

> One may consider examples from the chemical arts. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its function of lessening inflammation of tissues fails to

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[112] *Id.* at 1568.

[113] *Id.* at 1569.

[114] *Id.* at 1568. "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is."

[115] *Enzo*, 323 F.3d at 967-68.

[116] *Id.* at 968.

> distinguish any steroid from others having the same activity or function. Similarly, the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity. A description of what a material does, rather than of what it is, usually does not suffice. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described.[117]

The significance of *Enzo* for antibody inventions is that it indicated the Federal Circuit's intention to apply the legal principles of *Amgen*, *Fiers* and *Lilly* to all inventions, even when the structure and function differed from those in those earlier cases.[118] This is particularly relevant for antibodies because their function is somewhat more like that of the *Enzo* probes, namely, to bind to another material.[119] Thus, after *Enzo*, there was every reason to expect that the Federal Circuit would apply these written description legal precedents to antibodies.

VII. *Noelle v. Lederman*[120]

Unfortunately, this expectation failed to be satisfied in *Noelle v. Lederman*, the first case involving antibodies and the written description requirement. The *Noelle* case resulted from an interference between Lederman's '771 patent, which had an effective filing date of November 15, 1991,[121] and Noelle's '480 patent application, filed

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[117] Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 967-68 (Fed. Cir. 2002).

[118] *See* Paula K. Davis, *Questioning the Requirement for Written Description: Enzo Biochem v. Gen- Probe and Overly Broad Patent Cases* 37 IND. L. REV. 467 (2004).

[119] In *Enzo*, the material to which the claimed matter binds is genetic material from an organism, whereas for antibodies the material to which the claimed matter binds is called an antigen, which may be any of a broad range of materials, including small molecules and large complicated biological molecules such as proteins and genetic materials.

[120] Noelle v. Lederman, 355 F.3d 1343 (Fed. Cir. 2004).

[121] U.S. Patent No. 5,474,771 (issued Dec. 12, 1995).

November 1, 1996, which was a continuation of the '975 application, filed November 14, 1994, which was in turn a continuation of the '799 application, filed on February 14, 1992.[122]

Lederman had produced one antibody, called 5c8, which interfered with the activation of B cells by T cells, a phenomenon that could be important in cancer, among other diseases.[123] Lederman produced this single antibody by immunizing with particular human T cells. Lederman did not purify or characterize the antigen prior to making his antibody.[124] Noelle had isolated a protein from a mouse T cell line, characterized it, and produced an antibody against it, which he named MR1.[125] Noelle's antigen turned out to be the mouse's version of the same antigen involved in Lederman's patent.[126]

There was a single count in the interference, which read: "The monoclonal antibody of claim 1 of [Lederman's patent] or the monoclonal antibody of claim 42 or claim 51 of [Noelle's '480 application]."[127] Lederman's claim 1 recites "A monoclonal

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[122] U.S. Patent Application Serial No. 08/742,480 (filed Nov. 1, 1996); *see also Noelle* 355 F.3d at 1343.

[123] T cell and B cells are two immunological cell types.

[124] The antigen was later isolated and given the name CD40CR, which is also referred to as "CD40 counter receptor," "CD40 ligand," and "CD40L." *Noelle* 355 F.3d at 1345 n.3. Prior to its being characterized, Lederman called the hypothesized antigen T-BAM, which stood for "T-B cell activating molecule." The '771 patent acknowledges that T-BAM and what has now been recognized as CD40 ligand are the same. Lederman also referred to the antigen as the "5c8 antigen."

[125] *See Noelle* 355 F.3d at 1343.

[126] Other mammals beside the mouse and human, and perhaps even non-mammals, each have their own particular version of CD40CR, which may vary more or less in amino acid sequence compared with the mouse and human versions. In general, there is a fair degree of homology between a human protein and analogous proteins in other animal species and also a fairly high expectation that antibodies will cross-react with analogs from other animal species. *See supra* note 6.

[127] *Noelle*, 355 F.3d at 1345.

The terms "species" and "genus" are confusing enough without the complication that mice and humans are taxonomic species. The *Noelle* panel's opinion is rife with mistaken or confusing terminology which calls into question whether it knew it was dealing with species or genus claims, and what those claims actually covered. To avoid such confusion, the subject matter of Lederman's claim 1 and Noelle's claim 52 should be referred to as "antibodies that bind to human CD40CR," Noelle's claim 42

antibody which specifically binds and forms a complex with the 5c8 antigen located on the surface of activated T cells and thereby inhibits T cell activation of B cells, the 5c8 antigen being an antigen to which monoclonal antibody 5c8 (ATCC Accession No. HN 10916) specifically binds."[128] Claim 42 of Noelle's application reads as follows: "A monoclonal antibody or fragment thereof which specifically binds to an antigen expressed on activated T cells, wherein said antigen is specifically bound by the monoclonal antibody secreted by hybridoma MR1 which hybridoma has been deposited and accorded ATCC Accession No. HB 11048."[129] Claim 51 of Noelle's '480 application reads as follows: "A monoclonal antibody or fragment thereof which specifically binds CD40CR."[130] Claim 52 of Noelle's '480 application reads as follows: "The monoclonal antibody or fragment of Claim 51, wherein said CD40CR is expressed by activated human T cells."[131]

At a preliminary hearing, the Board of Patent Appeals and Interferences[132] denied Noelle's claims 51 and 52 the benefit of the 1992 filing date, finding that the claims "constituted new matter because they lacked adequate written description" as of that date.[133] Relying on *Lilly*, the Board required a "precise definition, such as structure,

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as "antibodies that bind to mouse CD40CR," and Noelle's claim 51 as "antibodies that bind to any CR40CR, regardless of the animal source."

[128] *Id.* at 1346. Because Lederman used a human T cell to create his 5c8 antibody, the court referred to his claim as the "human antibody."

[129] *Id.* Because Noelle's antigen was derived from mouse T cells, the court referred to his claim 42 as the "mouse antibody."

[130] *Id.* Noelle's claim 51 was referred to as the "genus claim" because it is not limited to a specific animal species.

[131] *Id.* Noelle's claim 52 can be considered to equivalent in scope to Lederman's claim 1.

[132] Hereinafter "Board."

[133] *Id.* The Board's statement that Noelle's application contained "new matter" is an odd way to analyze whether or not the benefit of his 1992 application could be obtained under 35 U.S.C. § 120. Section

formula, chemical name, or physical properties" of the antibody.[134] The Board found no interference-in-fact between the '480 application and the '771 patent and rejected several of Noelle's claims pursuant to 35 U.S.C. § 102(b) (2000)[135] The Board did not mention or rely upon Example 16.

The Federal Circuit affirmed the Board's finding that the '480 application was not entitled to the 1992 filing date for claims 51 and 52.[136] The court began its analysis by recounting the relevant written description case law prior to *Enzo*, including the requirement for a known or disclosed correlation between the function and structure of the claimed invention when the claim involves functional limitations.[137] However, rather than base its decision on this well-established precedent, the court instead said that it adopted text that does not even qualify as *dicta* from *Enzo* as precedent[138] The *Noelle* opinion stated that "the [*Enzo*] court proffered an example of an invention successfully described by its functional characteristics."[139] However, the example "proffered" was not an example whose merits the *Enzo* court needed to consider or indeed did consider.

The *Enzo* court actually stated:

> In its Guidelines, the PTO has determined that the written description requirement can be met by 'showing that an

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120 directs a determination under section 112, first paragraph, not under 35 U.S.C. § 132. How the Board confused section 112 with section 132 is all the more mystifying because the subsequent applications were continuation applications of the 1992 application.

[134] *Id.*

[135] *Id.* at 1347.

[136] *Id.* at 1350.

[137] *Id.* at 1348-49, referencing Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, (Fed. Cir. 1997), and other pertinent cases.

[138] *Id.* at 1349.

[139] *Id.*

> invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'[140]

The *Enzo* court then observed that the PTO "would find compliance" for a claim to an antibody.[141] It did not consider whether Example 16 would comply with the Guidelines or with the law. The *Enzo* court then turned back to the Guidelines, stating:

> Under the Guidelines, the written description requirement would be met for all of [Enzo's] claims if the functional characteristics . . . were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed. We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement.[142]

The *Enzo* court adopted a standard based on the law, which requires a known or disclosed correlation between function and structure.

However, the *Enzo* court never analyzed whether Example 16 conformed with this legal standard, which it stated immediately before the "proffered" example and then restated immediately following the "proffered" example. It never "proffered [Example 16 as] an example of an invention successfully described by its functional characteristics"

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[140] Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964 (Fed. Cir. 2002) (emphasis added).

[141] For example, the PTO would find compliance with 112, paragraph 1, for a claim to an "isolated antibody capable of binding to antigen X," notwithstanding the functional definition of the antibody, in light of "the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." (citing the Training Materials, *supra* at note 11, at 60)

Id.

[142] *Id.* (emphasis added).

but rather, proffered it as an example that the UPSTO would find compliant with the requirement for a written description of the invention. As discussed throughout this paper, the USPTO clearly did not apply the appropriate legal standard in analyzing Example 16. The court didn't indicate that it had actually analyzed Example 16 against the appropriate standard. Had the *Enzo* court needed to determine the adequacy of Example 16, it would have recognized that the factors that the USPTO relied upon are not relevant to a genus claim and it would have likely drawn the same conclusions that the authors draw in this article. Finally, the statement about Example 16 played no role in the analysis in *Enzo.* That court did not rely upon or adopt Example 16 as part of its reasoning or holding. In light of these several considerations, the statement about Example 16 in *Enzo* does not even qualify as dicta,[143] let alone, as the *Noelle* panel called it, "past precedent."[144] Under the Guidelines and the law, mere disclosure of a fully characterized antigen fails to provide a written description of a genus of antibodies that bind to the antigen because there is no known or disclosed correlation between function and structure.

Substantiating that the *Noelle* court erred in the justification for its result[145], it appears that the parties treated the claims as species claims and that the court failed to

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[143] Expressions of opinion which are not necessary to support the decision reached by a court are known as "dicta." 20 AM JUR 2D *Courts* § 39 (2004). Mere dicta are not binding under the doctrine of stare decisis. *Id. See also* BLACK'S LAW DICTIONARY, 454 (6th ed. 1990) ("*Dicta* are opinions of a judge which do not embody the resolution or determination of the court, and made without argument, or full consideration of the point, are not the professed deliberate determinations of the judge himself.") The sentence that the *Noelle* court cited from *Enzo* was not an opinion of the *Enzo* court, but rather an opinion of the USPTO, and was also irrelevant to the issue in *Enzo.* Therefore, the statement in *Enzo* about Example 16 has less persuasive authority even than *dicta.*

[144] *Id.* (emphasis added)

[145] The authors agree with the decision that Noelle was not entitled to the benefit of his 1992 prior application. Our point of disagreement with the court is its unnecessary and unwarranted attempt to elevate a gratuitous statement in *Enzo* to precedent. Furthermore, the authors believe that neither

appreciate that the USPTO analyzed the genus claim in Example 16 as a species claim, , as discussed above. For example, Lederman's reply brief states: "Here, the issue is about two patentably distinct species – [an antibody] to human CD40CR and [an antibody] to mouse CD40R. Thus, there is no possibility that the relevant public will face multiple infringement suits."[146]

The analysis of these claims as species claims raises serious questions about claim scope during litigation. If antibody claims are examined in the USPTO and treated in court as species claims for purposes of compliance with section 112, then consistency would require them to be treated as species claims, *i.e.* not as genus claims, during claim construction and infringement analysis.[147] Alternatively, if, as Lederman alleged during the appeal, Lederman's claim to an antibody that binds to human CD40CR and Noelle's claim to an antibody that binds to mouse CD40CR are "patentably distinct" and if "there is *no possibility* that the relevant public" will face suit from both Lederman's claim and Noelle's claim, then their respective claims may be quite limited in scope for another

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Noelle's nor Lederman's specifications complied *per se* with the requirement for a written description for any of the disputed claims, and that none of the disputed claims are valid.

[146] Noelle v. Lederman, No. 02-1187, Reply Br. at 6 (Fed. Cir. 2002) (emphasis added). Also, at oral argument, the following exchange occurred between the court and Lederman's counsel:

> The court: But wouldn't that disclose the entire genus [of antibodies against the CD40-CRs of all vertebrate species] though? If you know the specific antibody, wouldn't that disclose the entire genus?
>
> Lederman's counsel: No, it only discloses the mouse antibody that you have, because the human antibody structure will be different. The binding specificity will be different. In this case, the testimony is clear, the mouse antibody does not bind to the human. ."

Tr. at 16-17, Noelle v. Lederman, 355 F.3d 1343 (Fed. Cir. 2004) (emphasis added).

Upon request, the authors will provide a transcript of the oral argument, as well as copies of the briefs filed in *Noelle v. Lederman* including the brief *amicus curiae* filed jointly by Eli Lilly and Company, Protein Design Labs, and Bayer.

reason. This is so because many, if not most, antibodies that bind to a human antigen will also bind to the corresponding mouse antigen.[148] It is in fact usually preferred that therapeutic antibodies bind both to the targeted human antigen and also to the corresponding antigen of laboratory animal species because otherwise it is very difficult to test candidate therapeutic antibodies *in vivo* prior to clinical trials. Thus, under Lederman's own claim interpretation, a third party developing an antibody that binds to human CD40CR would not infringe his claim if the antibody also binds to mouse CD40CR.[149] Taking Lederman's assertions to their logical conclusion, any antibody that binds human CD40CR and also binds any other substance does not infringe Lederman's claim.[150] Such a claim may have no infringing embodiments.

With regard to the question of whether the Federal Circuit has now anointed Example 16 as precedent, the authors note that the *Noelle* panel did not actually apply the rule of Example 16 in reaching its conclusion.[151] Furthermore, considering that: 1) Example 16 does not comply with the Federal Circuit's well-established prior law on written description or with the Guidelines; 2) neither the *Enzo nor Noelle* panels analyzed whether Example 16 conformed with prior well-established precedents; 3) the

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[147] Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Cir. 2003); Spectrum Int'l Inc. v. Sterilite Corp., 164 F.3d 1372 (Fed. Cir. 1998); Lockwood v. Am. Airlines, 107 F.3d 1565 (Fed. Cir. 1997); Southwall Tech., Inc. v. Cardinal IG Co., 54 F.3d 1570 (Fed. Cir. 1995).

[148] *See supra* note 6.

[149] Neither would it infringe Noelle's claim to an antibody that binds to mouse CD40CR.

[150] *See supra* note 6.

[151] The rule of Example 16 states, essentially, that if the specification describes a new, non-obvious, and fully characterized antigen, then it meets the written description requirement for a claim to an antibody the binds to the antigen. The rule applied by the *Noelle* panel states that if the specification does not describe a new, non-obvious, fully-characterized antigen, then it does not meet the written description requirement for a claim to an antibody that binds to the antigen. A court should not announce a rule in a case where the result is not determined by that rule. To do so is to issue an advisory opinion, which is not a proper judicial function. *See* Teague v. Lane 489 U. S. 288 (1989).

"precedent" relied upon by the *Noelle* court was a sentence from *Enzo* that cannot even be considered to be dicta[152]; 4) the USPTO analyzed the genus claim of Example 16 as a species claim; and 5) the Guidelines (which the *Enzo* court adopted) do not include the training examples, the *Noelle* panel's "rule" is itself at best dicta. Therefore, the rule in *Noelle*, fashioned after Example 16, is neither binding precedent nor persuasive authority for the USPTO, the district courts, or other panels of the Federal Circuit. [153]

VIII. Proposed Alternative Analysis and Conclusion for Example 16.

In this section, we present a proposed alternative analysis and conclusion for Example 16, in light of the discussion and conclusions above.[154]

Analysis:

The claim is directed to the genus of all isolated antibodies that are capable of binding to antigen X. A review of the full context of the specification indicates that antibodies which bind to antigen X are essential to the operation of the claimed invention.

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[152] *See supra* note 143.

[153] Rhone Poulenc Agro, S.A. v. DeKalb Genetics Corp., 271 F.3d 1081 (Fed. Cir. 2001), *vacated, reh'g en banc, granted in part,* 284F.3d 1323 (Fed. Cir., 2002), and *cert. denied,* 539 U.S. 957 (2003). *See* Johnston v. IVAC Corp. 885 F.2d 1574 (Fed. Cir. 1989) (Where conflict exists between prior cases a panel should review the cases and reconcile them or explain the conflict. If this is not possible, a panel is obligated to follow the case law that is earlier in time.). *See also* Earl Maltz, *The Nature of Precedent,* 66 N.C. L. REV 367 (1988) (The degree to which a decision will control the outcome in later cases depends largely on the concreteness of the doctrine established in that case.) and JONATHAN SWIFT, GULLIVER'S TRAVELS Ch. 32 (1950) ("It is a maxim among these lawyers that whatever has been done before, may legally be done again: and therefore they take special care to record all the decisions formerly made against common justice, and the general reason of mankind. These, under the name of precedents, they produce as authorities to justify the most iniquitous opinions; and the judges never fail of directing accordingly.")

[154] The description of the specification and claim would not be altered, and are therefore not included. An earlier version of this proposed alternative analysis, as well as proposed alternative analyses for Examples 9, 14, and 15 were provided to the USPTO in October 2002. The authors will provide copies of these other proposed modifications upon request.

Persons skilled in the art understand that binding is a purely functional description, i.e. it describes what the antibodies do, not what they are.

No structure(s) responsible for the binding function appear in the specification. Furthermore, the specification fails to describe an actual reduction to practice of the claimed invention, fails to provide drawings or structural chemical formulas for the claimed invention; fails to describe partial structures of the claimed antibodies, and fails to provide a newly discovered correlation between the structure of the claimed antibodies and the function of binding to antigen X that would permit the skilled person to distinguish antibody structures that bind antigen X from those that do not.

Analysis of whether there is sufficient description of a "representative number of species" is meaningless because no species are disclosed. The genus inquiry is simply whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Such common attributes or features must be of the sort described by the "relevant identifying characteristics" – i.e. structure, physical and/or chemical properties, or functional characteristics coupled with known or newly disclosed correlation between structure and function.

The level of skill and knowledge in the art of antibodies at the time of filing was such that production of an antibody against any antigen, whether well-characterized or not, was generally conventional. Despite the skill and knowledge in the antibody art about their general structure and about how to generate antibodies, a search of the patent and scientific literature reveals that there was no correlation, let alone a strong correlation, that would allow one skilled in the art to predict with a reasonable degree of

confidence the antibody structures (variable region amino acid sequences) that are responsible for binding a described antigen.

The present application does not define any structural features, necessary for binding antigen X and commonly possessed by all members of the genus. Furthermore, function alone cannot suffice as an "identifying characteristic" because the claimed antibodies are not necessarily distinguished from the art. Because the genus is fundamentally defined solely by what the antibodies do, rather than what they are, there is no indication of possession of the genus. One skilled in the art cannot, for these reasons, visualize or recognize the identity of the members of the genus. Therefore, the disclosure is insufficient to show that applicant was in possession of the claimed genus.

Conclusion: The disclosure does not comply with 35 USC section 112 first paragraph because it fails to provide an adequate written description of the claimed invention, and therefore the claim must be rejected.

IX. Conclusions.

In this article, we analyzed Example 16 of the USPTO's Training Materials and concluded that Example 16 fails to meet the written description requirement of 35 U.S.C. § 112, first paragraph under both the Office's own Guidelines and under the case law as it applies to antibodies. The USPTO should delete Example 16 and inform its examiners that Example 16 should no longer be followed, despite *Noelle*. The USPTO should also adopt a new Example 16, similar to our proposal in this article, and should retrain its examiners to reject specifications like Example 16's under section 112, first paragraph.

Finally, neither the USPTO, the courts, nor the public should consider the *Noelle* decision to have any precedential value whatsoever for the legal proposition of Example 16.

Antibodies are chemical compounds, and even though they are large and complex chemical compounds, their structures have been completely amenable to description using amino acid sequences for at least twenty years. Thus, there is nothing unique about an antibody that commands a special rule like the one in Example 16 when it comes to its description. While various methods for making antibodies are known, knowledge of the conventional methods of making antibodies does not provide any information regarding the structure-function correlation that the law requires when using functional language in chemical claims.[155] Such methods merely constitute a research plan.[156] Until the plan is carried out, it is completely unpredictable and unknowable what *are* the yet to-be-discovered antibodies.[157] Furthermore, individual antibodies cannot be considered "representative" of a potentially broad, functionally-defined genus of antibodies that bind to an antigen. With no known correlations between an antibody's structure and its antigen binding function, it is impossible for one skilled in the antibody art to predict the

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[155] *See* Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916 (Fed. Cir. 2004); Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1566-67 (Fed. Cir. 1997); *In re DiLeone*, 436 F.2d 1404 (C.C.P.A. 1971).

[156] Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956 (Fed. Cir. 2002) and Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991).

[157] Results of immunizations are not reproducible and are subject to chance events that are not controllable. Each immunization will produce antibodies having varying structures and properties. Most will be commercially useless. *See* Jennifer Couzin, *Magnificent Obsession* 307 SCIENCE 1712-15 (2005) (This excellent article cogently conveys the difficulties that both Noelle's and Lederman's antibodies have faced during their pharmaceutical collaborators' efforts to convert their respective broad concepts of "an antibody that binds" into a safe and effective therapeutic antibody product. *Id.* Neither inventor's antibody has been found to be safe and effective. *Id.* at 1715. It appears that neither will be commercialized. *Id.* Finding and developing therapeutically safe and effective antibodies poses very challenging, real world problems that require real world inventions to overcome.) Unjustifiably broad patents such as the claim in Example 16 and the claims in dispute in *Noelle* merely stave attempts by others to innovate and discover commercially useful antibodies.

structure of any antibody, let alone all antibodies, that have the function of binding to an antigen. The fact that an antigen is "fully characterized" is irrelevant. Even a fully characterized antigen may be bound by a structurally diverse genus of antibodies.[158] Accordingly, the description of a single antibody (*e.g.* as in Noelle's '799 application) or of no antibodies (*e.g.*, as in the Panel's rule and Example 16) fails to comply with 35 U.S.C. § 112, first paragraph.

The Federal Circuit has stated that the purpose of the written description requirement "is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification."[159] The court has likewise recognized the troublesome consequences of allowing wholly functional claims on a yet-to-be-discovered genus of chemical compounds.[160] Such potentially broad claims will stifle entire fields of research and development. Yet, Example 16 and the *Noelle* panel's special antibody rule could permit broad, dominating rights to the discoverer of an antigen, thereby deterring the actual discovery of useful diagnostic and therapeutic antibodies. Perhaps equally chilling, the allowance of a claim to all antibodies on the basis of disclosure of a fully characterized antigen would create a significant, if not impenetrable, prior art barrier to the patenting of specific antibodies when they are subsequently discovered. Example 16

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[158] The magnitude of structural diversity in a genus of antibodies that bind an antigen can begin to be appreciated by comparison with the invalid genus claim to cDNA encoding for mammalian proinsulin in *Lilly*. In *Lilly,* there was exactly one proinsulin cDNA for each of the roughly 4,000 mammalian species (*i.e.*, human, rat, sheep, camel, donkey, elephant, etc.). However, for antibodies, each mammalian species could produce many thousands to many millions of distinct antibodies (*i.e.*, distinct variable regions) to an antigen, most or all of which would differ from the antibodies that all other mammalian species would produce. *See* Bryan M. Edwards, et al., *supra* note 53.

[159] Reiffin v. Microsoft Corp., 214 F.3d 1342, 1345 (Fed. Cir. 2000).

[160] *See Rochester*, 358 F.3d at 916; *Lilly*, 119 F.3d at 1559; Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993).

and the *Noelle* opinion, if followed, will cause patent stacking, multiple lawsuits, and disincentive to innovate in the antibody art.[161]

A truly mature field of art is one that has established relationships between structure and function, and therefore, a basis for claiming functionally what works. Antibodies are an empirical field, which has not established a describable relationship between an antibody's structure and its function of binding to something else. Therefore, antibodies are not validly described by stating that they "bind to antigen X."

[161] *See* P.H. Higgins, *Issues & Decisions Related to Discovery Assets in the Pharmaceutical Industry*, INTELL. PROP. TODAY, Apr. 2004, at 7.