COMMENTS OF ELI LILLY AND COMPANY ON THE REVISED INTERIM WRITTEN DESCRIPTION GUIDELINES

Eli Lilly and Company (“Lilly”) is pleased to offer the following comments regarding the Patent and Trademark Office's ("PTO's") recently published *Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, ¶ 1 "Written Description" Requirement* (“the Guidelines”) and the accompanying training materials entitled *Synopsis of Application of Written Description Guidelines* ("the Training Materials").

Having been involved in expensive and prolonged patent litigation that centered in part on the "written description" requirement for patentability, Lilly is particularly sensitive to the costs and burdens to the public of patents that contain claims to subject matter nowhere described in the patent specification. Our threshold comment to the PTO is, therefore, that the Guidelines make completely clear to patent examiners the important public policy objectives that are served by making reasonable and fairly based rejections for lack of written description in every circumstance where the decisions of the Federal Circuit justify such rejections. Where reasonable and fairly based rejections are made, applicants are afforded the opportunity to develop the law on "written description" through the *ex parte* appeal process. This route is far less expensive and far more satisfactory for both inventors and accused infringers than the painful process of *inter partes* litigation before a Federal court.

If the PTO can encourage such fairly based rejections to be made and if such rejections result in *ex parte* appeals, it is critical that appeals of this type be accelerated through the PTO so that definitive decisions of the Board of Patent Appeals and Interferences and, where appropriate, the Federal Circuit, can be developed in a timely manner. We urge the PTO to continue its outreach to the bar and trade groups to help identify such situations and accelerate the appeal process.

Lilly's review of the Guidelines has centered on the application of this “statutory requirement" to inventions in the chemical arts and life sciences. While we are encouraged that, through judicial decisions such as the *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997) (the *Lilly* case), the boundaries of the "written description" requirement have come into reasonably clear focus, we are concerned that some of the PTO's speculation on what is and is not a proper "written description" goes beyond any judicial sanction. Thus, instead of encouraging examiners to make reasonable and fairly based rejections, the Guidelines may instead encourage the issuance of U.S. patents that will later be invalidated on completely foreseeable "written description" grounds.

As one example of the problematic nature of the Training Materials, we refer to Example 7. If an EST claim is made with "comprising" language and, therefore, is completely "open ended," its scope will be potentially huge. If this claim is deemed to lack a "written description," because no complete gene sequence is disclosed which contains the claimed EST sequence, this written description defect cannot be remedied merely by the disclosure of a *single cDNA species*. Since such an open-ended claim could encompass many different DNA sequences, disclosure of

a single cDNA is not sufficient to describe the characteristics of the genus. To find such a claim adequately described would be flatly inconsistent with the test set out in the Guidelines indicating that a "representative number of species" would be needed where a broadly crafted claim is presented. Moreover, such a result (curing a "written description" for a broad generic claim by a specific disclosure of a single species) would be difficult, if not impossible, to reconcile with the Federal Circuit's decision in the *Lilly* case.

This leads us to the conclusion that the PTO should exercise extreme caution in setting out "guidelines" for what is patentable, as opposed to clearly setting out circumstances where a rejection would be fairly and reasonably based.

Second, we have a general concern for the PTO's position pertaining to patent claims for protein sequences—and, in particular, to claims directed to protein variants (and the DNA molecules encoding them) having amino acid sequences with a certain *percent identity*, *similarity*, or *homology* to the native protein. We are concerned that the existing guidelines and training materials do not apply the proper standard for written description to such claims in light of the Federal Circuit's decision in the *Lilly* case.

Example 14 of the Training Materials illustrates the application of the written description requirement to the following generic claim:

> A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A→B.

Under the Training Materials as currently drafted, a generic claim similar to Example 14 would be adequately described under Section 112, ¶ 1, because (1) "[t]he single species disclosed is *representative of the genus* because all members have at least 95% structural identity with the reference compound," and (2) because of the limitation requiring the stated compounds to catalyze the reaction of A→B. See Training Materials at 54. (Emphasis added). In Lilly's view, the PTO's proposed approach merely substitutes one linguistic formulation ("percent identity," "similarity," or "homology" coupled with a required biochemical property) for another linguistic formulation (encoding a particular class of proteins) found insufficient to satisfy the requirement of an adequate written description under the Federal Circuit's decision in the *Lilly* case. While different sets of words have been used, the fact remains that no generic invention has been made, disclosed, or described.

We generally agree with the conclusion in the PTO's Guidelines that the written description requirement cannot be satisfied for claims to proteins and DNA sequences by simply disclosing a proposed function without describing a corresponding structure that carries out that function. Guidelines at 71436. In addition, we generally agree that "[i]n an unpredictable art [such as the characterization of novel protein and DNA sequences] adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." *Id.* We disagree, however, that the boundary between predictability and unpredictability in this field can be set at some arbitrary, even seemingly high, percent similarity.

In *Lilly*, the Federal Circuit held that a genus of cDNAs could be described by recitation of a representative number of species or by recitation of structural features common to a substantial portion of the genus. *See* 119 F.3d at 1568-1569. The Court based its holding on its recognition that the mere recitation of a biological property or function, without a representative disclosure of working species or common structural elements, cannot suffice to describe a genus of cDNA variants—and, hence, the protein variants they encoded. *Id.*

In *Lilly*, the Federal Circuit held invalid claims directed to "vertebrate insulin cDNA" and "mammalian insulin cDNA" because neither genus was adequately described by the disclosure of the single species, rat insulin cDNA, in the patent specification. However, contrary to the reasoning set forth in *Lilly*, the Training Materials suggest that claims to analogous proteins could be adequately supported by the disclosure of a single species by a mere change of claim wording from "mammalian insulin" to "protein variants at least 95% identical to insulin." This change, however, is little more than a different linguistic construct fashioned over the same inadequate description. In the *Lilly* case, there was no manner in which a person skilled in the art could identify the things – the chemical structures – that were "mammalian proinsulin cDNAs." No structures, no described genus. Example 14 embodies a fully analogous defect: What are the structures of the 95% homologous proteins that have the required catalysis biochemical activity? They are unknown and unknowable from even the closest inspection of a patent specification disclosing only one, or even a few, biochemical species.

A claim to a genus of protein variants *at least 95% identical* to a native protein may be, in form, narrower than a claim to *all variants* having the native protein's function. However, the claimed genus in substance still encompasses an enormous number of species with potentially widely diverse properties and describes little in the way of common structural features of the claimed proteins. Indeed, the genus of all variants at least 95% identical to a protein of 300 amino acids would encompass every species having between 1 and 15 amino acid changes to any of the 20 naturally occurring amino acids, at any location in the protein chain. Mathematically such a genus would potentially encompass *thousands of trillions* of chemical compounds, even assuming that no gaps, truncations, extensions, or insertions are made to the chain. On the DNA level, even greater numbers of compounds are involved. If only a few hundreds of billions of proteins within this mass of thousands of trillions of compounds are catalytically active, then the structures of the compounds comprehended by the claimed genus are mere needles in a haystack. Finding one needle is no description of the remainder

Hence, the mere use of the formulation "95% identical" instead of "mammalian" or "vertebrate" does not meaningfully distinguish the claimed genus in terms of its structural rather than functional features. Merely adopting different claim language cannot substitute for an actual inquiry into the extent to which a *generic invention* is *disclosed* in an application. The proper focus must be on the disclosure and what it teaches to one of ordinary skill in the art.

The PTO would stand on sound public policy ground by taking a fairly based and reasonable position that the technical state of the art in protein structure and function points to the invalidity of percent identity or homology claims, such as those in Example 14, even where the percentage homology is very high – unless the applicant provides commensurately substantial guidance from the specification as to structural features of the genus. Despite the presence of 95% common amino acids among the various species, a claim to such protein variants would be expected to fold into many different secondary structures – and exhibit divergent biology and biochemistry. Again, assuming the variants differed in up to 15 of 300 amino acids (95%), entire structural domains in the variant proteins would be expected to be added, disrupted, or eliminated depending on the location and nature of the 15 changes in the sequence. Current knowledge of the relationship between amino acid sequence and protein secondary structure and function is inadequate to support broad assumptions about the structural features shared by the many species of proteins encompassed by a genus of biologically or biochemically active variants 95% identical to a native protein.

Regarding the potentially substantial difference in properties allowed by changes well within the 95% cutoff proposed by the PTO, one need look no further than the genetic defect responsible for sickle cell anemia. There, a change in a single nucleotide converts the encoded hemoglobin molecule from one with the natural function to one that carries with it properties associated with debilitating disease and even death. Many other examples can be found in the literature. Indeed, the genome of the chimpanzee is approximately 99% homologous to the human genome and yet there are obvious substantial differences between the two species.

Finally, the Guidelines state that there is a strong presumption that original claims meet the written description requirement and that rejection of such claims should be rare. At least for DNA/protein claims, the holdings of *Fiers* and *Lilly* would seem to indicate that the PTO's comments relating to original claims is an overstatement of the law. These cases clearly indicate that a claimed genus of DNA sequences must be adequately described in the specification whether or not the claim was originally found in the application.

In light of the Federal Circuit's interpretation of the written description requirement of Section 112, first paragraph, we would urge the PTO to require more than the disclosure of a single sequence from applicants seeking claims to protein variants of a given percent identity and function. Such claims should be supported by adequate recitation of the specific collection of structural features of the genus that would allow it to be distinguished from others. We would also urge that the Training Materials, and Example 14 in particular, be modified to reflect this requirement. We would urge the Guidelines and Training Materials be refocused on when and where to reject because it is fair, reasonable, and in the public interest to do so.