

DRAFT

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Box 8
Commissioner of Patents and Trademarks
Patent and Trademark Office
Washington D.C. 20231

Attention: Scott A. Chambers, Associate Solicitor

Comments on Interim Guidelines on the Written Description Requirement

The written comments presented herein represent the views of the National Institutes of Health (NIH). The NIH is the lead agency within the Public Health Service (PHS) in matters of technology transfer. In addition to providing patent and licensing services to all Institutes and Centers comprising the NIH, PHS lead agency status encompasses coordinating and facilitating technology transfer policy functions with the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). Central responsibility within NIH for these technology transfer functions has been delegated to the Office of Technology Transfer (OTT).

Summary

The U.S. Patent and Trademark Office (PTO) has set forth a workable outline for analyzing applications for compliance with the written description requirements. There appears to be significant deficiencies, however, in analyzing the proper relationship of the preamble, transition phrase, and claim body to determinations of genus versus species claims. This determination is particularly critical to the application of the open-ended transition phrase "comprising" to claims involving nucleic acids and amino acids. A number of examples are presented to clarify this relationship. Due to the highly controversial nature of Expressed Sequence Tag (EST) applications in the biotechnology community and the relevancy of these written description considerations to the patentability of EST claims employing comprising language, the NIH requests that this issue be addressed specifically in the final guidelines.

Introduction and Background to Federal Transfer of Biotechnology:

A) Legislative Mandate for Federal Technology Transfer

The Bayh-Dole Act of 1980, Pub. L. No. 96-517, 94 Stat. 3015, as amended, permits recipients of federal grants and contracts to retain intellectual property title to their

inventions. This act also permits exclusive licensing of Government-owned inventions. In October 1986, Congress enacted the Federal Technology Transfer Act (FTTA), Pub. L. 99-502, 100 Stat. 1785, which amended the Stevenson-Wydler Innovation Act of 1980. The FTTA, as amended, stimulates transfer of Government-owned technology by offering incentives to both federal laboratories/scientists and collaborating partners in universities, foundations (both profit and non-profit) or private industry. With regard to intramural research, the FTTA obliges government scientists to report inventions having commercial or health benefit potential for transfer to the private sector. To facilitate this obligation, the Act provides incentives comprising cash awards and distribution of a portion of licensing royalties back to the laboratory and inventors.

B) NIH Advancement of Technology Transfer Mandate

The NIH has engaged in considerable technology transfer activity consequent to the initiatives promulgated by the FTTA. Since fiscal year 1987, the NIH has received over 900 issued patents, executed over 1,300 license agreements, generated about 200 million dollars in royalties, and entered into about 400 CRADAs. While significant, these activities reflect transfer of only a fraction of the cutting-edge invention portfolio generated by the world's preeminent public entity dedicated to the advancement of health care.

Beyond this intramural research contribution, the NIH funds biomedical research at universities and contractor-operated research facilities via research grants and contracts. Funding of extramural grants and contracts constitutes approximately 90% of the 13-plus billion dollar annual budget provided NIH for health research and development. As a result of these two contributory streams, the NIH is the world's leading source and underwriter of biomedical inventions.

A significant proportion of the NIH's intramural research and extramural funding is directed to genomics. This involvement extends to numerous aspects of genomic diagnostics, therapeutics, and sequencing. Consequently, NIH is a major stakeholder in the genomic arena and has commensurate interest in any proposed guidelines related to the examination and patentability of biomedical inventions describing nucleic acid and amino acid sequences.

C) NIH Technology Transfer Policy Issues

NIH technology transfer policy related to both intramural inventions and funding of extramural research are guided by the NIH mission to advance the public health. When significant intellectual property issues arise within the biotechnology community that impinge upon that public health mission, NIH exercises its leadership and stewardship role.

A recent intellectual property concern in this regard relates to access by the non-profit research community to research tools. NIH initiated a number of actions toward ameliorating this concern. First, NIH modified its intramural patent and licensing policies to insure that NIH's own technology transfer processes facilitates unencumbered access to research tools. Second, the NIH Director convened a Research Tools Working Group of technology transfer representatives from government, academia, and industry to survey and analyze the issue, and recommend steps to facilitate the unencumbered flow of research tools and biological materials to, from, and within the research community. Release of NIH guidelines implementing the recommendations of this work group is scheduled for the end of this calendar year. Third, NIH and DuPont Pharmaceuticals Company recently negotiated a Memorandum of Understanding providing non-profit researchers free access and elimination of "reach through" options in non-commercial research licenses related to a broad based research tool (Cre-lox technology). The agreement satisfies industry's legitimate intellectual property and commercial interests; yet satisfies the NIH concerns regarding encumbrance of research tools to the non-profit sector. It is expected that the general terms of this agreement will become a model in the academic and government research communities. Fourth, NIH and various members of the biotechnology and pharmaceutical communities have been engaged in dialogue to find ways for industry to support and augment NIH's massive genome sequencing initiatives. These initiatives include sequencing and placing into the public domain the entire human genome, as well as libraries of expressed sequence tags (ESTs) and single nucleotide polymorphisms (SNPs). The NIH considers ESTs and SNPs examples of genomic research tools which need to be made available for unencumbered research to advance the public health.

Summary of Correspondence with the PTO Regarding Concerns Related to Patenting of EST Sequences

As indicated above, the NIH has policy interests in partial DNA sequences (i.e., ESTs) whose primary utility in the research community is as a tool to probe for unknown genes. The NIH has voiced its intellectual property concerns regarding ESTs in various fora, including communications to the U.S. Patent Office (PTO) and the Council of the National Academy of Sciences (NAS). The following is a synopsis of relevant considerations derived from such communications.

Soon after its February 14, 1997 public announcement that the PTO considered ESTs patentable subject matter based upon their utility as probes, the Director of NIH (Dr. Harold Varmus) communicated his deep public health concern that such patents may have a chilling effect within the genomics industry. Dr. Varmus' communication was supplemented by a letter from the NIH Office of Technology Transfer detailing the NIH position on the utility issue of ESTs disclosed as probes for unknown genes. This supplemental letter also discussed enablement (undue breadth) issues raised by potential EST claims containing open-ended "comprising" language which broadens scope by introducing random sequences of indeterminate length. This undue breadth scenario was

compared to Examples A and B in the PTO Guidelines and Training Materials regarding enablement in chemical and biotechnical applications. Copies of these letters are enclosed.

On April 2, 1997, Commissioner Lehman responded to these NIH communications. The Commissioner acknowledged the NIH concerns and indicated, "[m]ere allegation of the utility of an EST as a probe without further disclosure is not sufficient to meet the utility and enablement criteria." Commissioner Lehman elaborated that potential EST utilities related to forensic identification, tissue type or origin identification, chromosome mapping, chromosome identification, and tagging a gene of known and useful function. These utilities were indicated to be potentially enabled "if supported by a sufficient disclosure." Related to the scope of EST claims, the Commissioner stated, "[u]nder appropriate and limited circumstances, claims of a perceived broad scope that are adequately supported by the disclosure under 35 USC 112 and the state of the art may be patentable,..."

The above exchange of communications and other issues related to patenting of research tools were discussed at the Council of the NAS. The NAS is a society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Under its charter granted by Congress in 1863, the NAS is mandated to advise the federal government on scientific and technical matters.

The NAS has a long standing interest in the intellectual property aspects of research tools used in molecular biology. Since 1993 the NAS has conducted two major workshops on the issue, including one on ESTs, and has published a 1997 National Research Council report on the subject of research tools.

Pursuant to these discussions, Dr. Bruce Alberts, President of the NAS, communicated also with Commissioner Lehman. Dr. Alberts' June 19, 1997 correspondence reiterated the concerns of NIH, and sought clarification of the Commissioner's statement above regarding the possibility of EST claims of broad scope. Furthermore, Dr. Alberts urged the PTO to question the potential enabled utilities proposed in the Lehman letter to Harold Varmus. Communicating on behalf of the Council of the NAS, Dr. Alberts stated the following:

[d]isclosure of DNA sequence alone is plainly insufficient to enable scientists to use an EST for any of these purposes. Data about the exact chromosomal site from which a DNA fragment arose are needed for mapping; data about unique expression in a particular tissue or physiological state are needed for tissue typing or diagnosis; and data about polymorphism among individuals are needed for forensic uses.

In the PTO response to this NAS representation of the state of art related to the enablement of the indicated EST utilities, Commissioner Lehman indicated the following:

The NAS has urged the USPTO to question whether the EST patent applications have applied a sufficient enabling disclosure regarding exact chromosomal sites, unique expression in a particular tissue, or polymorphism among individuals to enable the use of these DNA sequences for mapping, tissue typing, or forensic use. Considerations such as these are clearly within the scope of 35 U.S.C. §112 and are fully considered in accordance with the *In re Wand's* decision in the enablement determination of every claimed invention.

In each of the above communications from the Commissioner, the PTO appears to acknowledge the relevance of the NIH and NAS legal and scientific positions regarding the utility and potential scope of EST claims. As appropriate, the PTO responses imply the issues would be examined on a case by case basis consistent with the relevant case law and published PTO guidelines on utility and enablement. More recently, however, PTO presentations at various public meetings, such as the 1998 Annual Meeting of the Biotechnology Industry Organization (BIO), indicate a perceptible hardening regarding the EST issue. Despite its predisposition against *per se* rules in the examination process, the PTO appears to be contemplating accepting broad disclosure of any or all of the above identified potential utilities as satisfying the 35 USC 101 requirement for all claimed ESTs. Furthermore, such presentations indicate generalized willingness to apply broad scope "comprising" language in EST claims. NIH finds most disturbing these representations of an apparently evolving policy toward accepting utility and broad claim scope *per se* for EST patent applications in light of significant NIH/NAS legal and scientific arguments that should militate against such general considerations and conclusions. The NIH believes developments in case law on written description militate also against the issuance of broad EST claims containing open "comprising" transition language.

It was anticipated that the pending interim guidelines on the written description requirement of 35 USC 112 might shed light on the logic underlying the PTO's intentions regarding these controversial issues. However, specific mention of this class of invention involving nucleic acid sequences is conspicuously absent from these interim guidelines. The failure to address this subject is particularly disturbing considering the huge number of ESTs pending at the PTO, and the serious concerns raised about ESTs by varied groups interested in the well being and continued development of the biotechnology community. In addition to the public health issues raised by the NIH and the technical and science policy issue raised by the National Academy of Sciences, BIO and numerous biotechnology and pharmaceutical companies have also raised concerns about issuance of broad EST patents

The NIH requests that written description issues related to EST claims be formally addressed, including examples, in the Final Guidelines on Written Description. To the extent there are significantly divergent opinions expressed to the PTO regarding written description issues related to ESTs, it would be appropriate to enumerate these views, as well as the PTO's evaluation of same in arriving at its final guideline determinations. Toward that end, the NIH submits the following comments related to the written description guidelines generally, as well as their application specifically to EST claims.

Specific Comments on the Interim Guidelines

A) General Outline of Criteria to be Analyzed

The PTO is commended for its clarity regarding the basic outline of steps and points for consideration in determining whether a disclosure complies with the written description requirement of Section 112, first paragraph. As indicated, the written description requirement is satisfied when the specification describes the claimed invention in sufficient detail to conclude the inventor had possession of the claimed invention at the time of filing.

The interim guidelines succinctly indicate that a proper analysis requires evaluation of the entire application including the specification and the scope of each claim. This evaluation is conducted from the perspective of one skilled in the art at the time the application was filed. Each claim is given its broadest reasonable interpretation, and all parts of the claim (i.e., preamble, transitional phrase, and body) are considered. Also analyzed are the field of the invention and the level of predictability in the art; wherein the level of predictability in the art is inversely related to the amount of disclosure necessary to demonstrate possession of the claimed invention. It is noted that this array of elements markedly overlaps the *In re Wands* factors for undue experimentation employed when determining enablement¹.

The guidelines instruct that each species claim should be analyzed to determine if either the entire structure is described or sufficient identifying characteristics are disclosed. For each genus claim an analogous determination is made regarding the presence of a representative number of species examples described either by complete structure or sufficient identifying characteristics. Again, validating a genus claim by evaluating a representative number of species is analogous to the procedure used to determine enablement of a genus claim. See identification of this analogy recited in *University of California v. Eli Lilly and Co.*²

In this regard, the general overview provided by the interim guidelines represents well the relationship between written description and enablement. In particular, it reflects how the

¹ *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988)

² *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)

written description requirement is broader than the enablement requirement of Section 112, which is subsumed within the description of the invention and, thereby, satisfies a separate and distinct purpose in demonstrating possession of the invention³.

B) Genes, mRNA, and cDNA as Preamble Terms

The interim guidelines go to particular lengths to establish a distinction between two sets of preamble terms. One set consists of the terms gene, mRNA, and cDNA. The PTO interprets each of these terms as representing a small genus of specific structures which include, in addition to the amino acid coding region, such elements as promoters, enhancers, and other regulatory elements. It is the PTO contention that all such subcomponents of these preamble terms must be described to satisfy the written description requirement.

It is respectfully submitted that this is an *ad hoc* interpretation which establishes *per se* definitions of molecular biology terms which commonly are used to mean different things depending on the particular context. Contrary to the interim guideline's interpretation, the most generally used context of these terms refers only to the coding portion of the molecules. This context is supported both in common patent usage and case law.

Judge Rich provided an extensive background section on the molecular biology involved in protein synthesis in *In re O'Farrell*⁴. Nowhere does Judge Rich make the distinctions regarding the substructures suggested above. More recently, Judge Lourie provided an expanded background description of this topic in *In re Deuel*⁵. In fact, that background section recites, "The claimed invention relates to isolated and purified DNA and cDNA molecules encoding..." While this case resolves an issue of obviousness, it derives its decision based upon analogous considerations regarding treating DNA/cDNA claims as chemical structures that must be defined by their specific structure (e.g., sequence), rather than by their function or method of making. Needless to say, no distinction in cDNA substructure was given any consideration in evaluating the claims. Finally, Example N: DNA in the previously mentioned "Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications" describes and claims both DNA and cDNA molecules. The cDNA claims are in open "comprising" format reciting a specific nucleotide sequence or fragments of a specified length. It is clear from this common claim usage that the cDNA is intended to represent, and be synonymous with, the coding region of the molecule. Respondent is not aware of any patents where the substructure composition of cDNA, mRNA, or genes was a significant issue in determining aspects of patentability, or in determining what structures were deemed in the possession of the inventor.

³ *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991)

⁴ *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988)

⁵ *In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995)

Adoption of the PTO's new definition of cDNA, mRNA, and gene for purposes of written description considerations potentially would reek havoc in the biotechnology community. Myriad patents have issued claiming genes, cDNAs, and mRNAs without regard to the PTO's new interpretation of claim language. Correspondingly, numerous business arrangements have been predicated upon such claims. Most, if not all, of those patents and business deals would be undermined by uncertainty were these interim guidelines adopted. The problems invoked in the biotechnology sector would far outweigh any benefit in waging a semantic debate regarding a *per se* definition regarding the structure of these molecules. The specifics regarding the context of usage in each individual case will be more instructive toward determining possession of the claimed invention.

Perhaps as a consequence of this curious interpretation of molecular terminology, the interim guidelines provide a confusing representation of the following claim: "A gene comprising SEQ ID NO: 1". This claim is described as being viewed as a species claim with a combination/subcombination relationship between the preamble and the body. In reality this is a genus claim based upon the open "comprising" transition phrase. This claim truly would be a species claim if redrafted using the transition phrase "consisting of". Contrasting these two situations, it is clear that the genus/species nature of a claim is driven by the nature of the transition phrase and the body of the claim, not by the preamble.

If the body of the claim does not correspond well with the preamble term, this may represent a problem of definiteness under 35 USC 112, second paragraph; not the first paragraph of Section 112. A more appropriate consideration is if the "comprising" term enlarges the scope of the SEQ ID NO: 1 structure such that it is not enabled or does not support possession of the structure under the written description requirement.

C) Nucleic Acid, DNA, and RNA as Preamble Terms

By contrast, the interim guidelines propose that substitution of more general preamble terms, such as composition, nucleic acid, DNA, and RNA somehow creates a genus claim. The specific example of this phenomenon is the claim construction, "A nucleic acid comprising SEQ ID: 1." The interim guidelines interpret the generic nature of this claim to reside in the term "nucleic acid." Each member of the genus "nucleic acid" is considered under the interim guidelines to be a combination containing the subcombination "SEQ ID NO: 1" (which is a fragment of the nucleic acid). The interim guidelines proffer that the generic nature of the term "nucleic acid" prevents a written description problem because one skilled in the art can readily envision a sufficient number of members of the claimed genus to provide written description support for the genus. A footnote "16" to pages 1405-1406 of the previously mentioned University of California v. Eli Lilly and Co. CAFC case is recited to support this proposition.

Respondent has carefully reviewed this case, including the specified pages, and finds no mention of written description support for generic claims arising from envisioning genus members based on preamble terms such as composition, nucleic acid, DNA, or RNA. The issue addressed on pages 1405 to 1406 of this case is that a disclosure of rat insulin cDNA is not sufficient to support generic claims to vertebrates or mammals. Substitution of the term nucleic acid for cDNA does not remedy this deficiency. There is nothing in the term nucleic acid that envisions sufficient numbers of insulin sequences corresponding to different vertebrate or mammalian species so as to provide written description support for the genus. The only way to remedy the deficiency is to disclose the actual sequences of a representative number of species to support the genus; rather than wordsmith the preamble of the claim.

D) What Defines Species Versus Genus Claims?

The distinction between species and generic claims is an important concept in the interim guideline, because genus claims require additional considerations. At least in unpredictable arts such as chemical and biotechnology inventions, genus claims additionally require sufficient description of a representative number of species to support possession (written description) of the genus. The interim guidelines provide little direction and guidance toward distinguishing species from genus claims. As discussed above, where the interim guidelines address this issue between preamble terms such as cDNA and DNA, they appear to confuse the issue more than elucidate it. The generic nature or scope of a claim is determined by the interplay of the transition phrase and the limiting embodiments of the material representing the body of the claim. The following examples will attempt to illustrate this.

1) On page 1406 of *University of California v. Eli Lilly and Co.*, Judge Lourie sets forth a description of a classical chemical generic claim.

[i]n claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.

In such a scenario, the generic formulae may be a three-ring heterocyclic nucleus of specified structure with two defined substituent R-groups (e.g., halogen and alkyl R-groups) at specified locations on the nucleus. Species are envisioned or identified by substituting different members of each R-group (e.g., substituting a bromine or a chlorine as the halogen R-group). Enlarging the breadth of the claim by using "comprising" as the transition phrase permits inclusion of other unrelated compounds or materials (e.g., a solvent) without changing the generic formula. Such included unrelated compounds or

materials need not be identified to satisfy the written description requirement. Similarly, choice of preamble phrases generally will not change the nature of the defined generic formula. For example, defining the preamble broadly as a composition, rather than a three-ring heterocyclic compound, does not permit adding a fourth ring or a third R-group to the defined nucleus. A person skilled in the heterocyclic art can distinguish this generic composition and species encompassed therein from others by its formula. Accordingly, the formula is an adequate written description of the claimed genus.

2) The first example in Section C(2) of the interim guidelines describes an isolated double-stranded DNA defined by sufficient identifying characteristics (i.e., size, cleavage map, and source from which the DNA is derived) that one skilled in the art would recognize from these characteristics that the inventor was in possession of the claimed material. This is a species claim regardless the nature of transition phrase associated with the claim. Changing the transition phrase from "consisting of" to "comprising" would broaden the scope of the claim by permitting additional unstated subject matter, but would not change the combination of characteristics that define this species of double stranded DNA.

3) The relationship described in the examples above differs dramatically when the formula defining the invention in the body of the claim is a nucleic acid or amino acid sequence. In these cases, "consisting of" transitional language limits the claim to the recited nucleic acid or amino acid sequence. Substitution of "comprising" transitional language creates a generic sequence formula which permits additional unstated subject matter as previously. However, this open-ended language also permits the length of the nucleic acid or amino acid sequence to be expanded at either or both ends. The magnitude of this lengthening of the original structure is indeterminate, and the identity of each added nucleotide or amino acid is unknown and random. The magnitude of this type of modification of the core sequence can be tempered by limiting the size of the claimed moiety (e.g., nucleic acid limited to 40 nucleotides), and by limiting the nature of the additional sequence (e.g., at a defined position in the amino acid sequence permit only lysines to be added to the carboxy end of the molecule).

The interim guidelines succinctly explain the inverse correlation between predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. A generic formula must provide a reasonable expectation that species within that genus structure will exhibit similar function corresponding to the disclosed utility(ies) of the invention. Sufficient examples of species must be provided by the disclosure to support and validate possession (written description) and enablement of that level of predictability between structure and function. The broader the generic structure and/or more unpredictable the state of the art related to the invention, the more examples are required of the disclosure to establish that relationship. To better understand the dramatic consequences to the predictability of this structure-function relationship caused by comprising language in nucleic acid or amino acid sequence formulae, it may be

instructive to analogize the effect of comparable modifications to more traditional generic chemical formulae.

In the context of example 1 above (generic three-ring heterocyclic formula), the analogous enhancement of claim scope would involve adding an indeterminate number of undefined rings to the nucleus of the molecule or adding an indeterminate number of new R-group substituents of undefined nature onto the nucleus. Such additional rings or R-groups would dramatically alter the structure-function relationship defining the claimed molecule. In other words, four-ring, seven-ring, or ninety-ring heterocyclic compounds would not be expected to exhibit the same function(s) or utility(ies) characteristic of a three-ring heterocyclic structure. Similarly, three-ring heterocyclic compounds having five, nine, or twelve substituent R-groups of undefined nature would not be expected to exhibit the same functions as species encompassed by the two defined R-groups of example 1. It is unlikely that any disclosure could support the possession or enablement of essentially an infinite array of possible structures in support of a real world patentable utility.

Examples A and B in the previously mentioned Training Materials for Enablement reinforce aspects of this marked enhancement of structural scope created through use of "comprising" transitional language in claims drawn to nucleic acid sequences. Both examples present related fact patterns involving claims reciting open "comprising" language and Markush groups containing specific Sequence ID numbers corresponding to three disclosed nucleotide sequences. Both examples rely upon hybridization involving the claimed sequences to effect the disclosed utility. Both examples cite a pair of literature references, Sambrook et al. and Wallace et al., for their teaching that mismatches within an oligonucleotide probe impart unpredictability to the hybridization process. Both examples explain how the "comprising" language markedly broadens the scope of the nucleic acid sequences by introducing additional random sequence of indeterminate length. In view of the teachings of Sambrook et al. and Wallace et al., the introduction of random base sequence was deemed to skew the predictability of structure to function sufficiently to render the claims nonenabled. Both examples recommended limiting the claim scope by use of "consisting of" transitional claim language to satisfy the undue breadth problem.

The independent and distinct nature of the written description and the enablement requirements of Section 112, first paragraph contemplates situations where a chemical formula or a nucleic acid/amino acid sequence is described adequately so as to demonstrate possession at the time of filing, but that same disclosure fails to teach how to make or use (enable) the possessed invention. The distinctions between these two elements of Section 112 converge, however, where lack of enablement results from undue breadth of claim structure (e.g., Examples A and B, above). Circumstances of undue breadth likely will invoke also a deficiency in the written description requirement. In both cases, there is failure to disclose sufficient numbers of species corresponding to the overly broad genus to support possession or enablement. The disclosure required for

both possession and enablement is inversely correlated to similar levels of predictability in the art. Additional considerations drawn to the scope of claims, nature and field of invention, and level of skill in the art are similar when analyzing the same overly broad claims for possession and enablement.

This convergence of enablement and written description considerations is exemplified in *In re Fisher*⁶. Claim 4 of *Fisher* is drawn to an adrenocorticotrophic hormone (ACTH) preparation. The claim construction involves open-ended "containing" language (analogous to comprising) with a limitation that the preparation is characterized as containing polypeptide of at least 24 amino acids having an enumerated sequence. The court indicated the open ended claim construction broadens the claim such that "the claimed subject matter is in no way limited by the presence, absence or sequence of amino acids beyond the 24th position." While this claim language was deemed definite under the second paragraph of Section 112, it raised questions of sufficiency of disclosure under the first paragraph of that section. The court ruled the application failed to support ACTH preparations with other (i.e., greater) than 39 amino acids. Consequently, the specification was deemed to lack sufficient supporting description to comply with the requirements of 35 U.S.C. 112, first paragraph. Related to this lack of a sufficient supporting description, the claims were found also to be not enabled. This exemplifies the "broader" nature of the description requirement, wherein the lack of description was manifested also in the inability to make or obtain the invention.

The rationale for finding a written description deficiency in open-ended nucleotide/amino acid sequence claims, wherein the range of possible sequence structures far exceeds those taught or contemplated by the specification is in concert with a line of more recent decisions from the CAFC. Specifically, the decisions in *Amgen v. Chugai*⁷ and *Fiers v. Sugano*⁸, as well as *University of California v. Eli Lilly and Co.* require a close correlation between defined sequence structure and the written description requirement.

Consistent with requiring precise and narrow disclosure of nucleic acid and amino acid sequences for purposes of written description and enablement, the CAFC also narrowly interprets nucleic acid structure considerations relative to determinations of obviousness. See *In re Bell*⁹ and *In re Deuel*. Referring to *In re Bell* and *In re Deuel*, the CAFC in *University of California v. Eli Lilly and Co.* stated the following position on the relationship of written description of sequences to reaching conclusions of obviousness:

[a] prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the

⁶ *In re Fisher*, 166 USPQ 18,23 (CCPA 1970)

⁷ *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18USPQ2d 1016 (Fed. Cir. 1991)

⁸ *Fiers v. Sugano*, 25USPQ2d 1601 (Fed. Cir. 1993)

⁹ *In re Bell*, 26 USPQ2d 1529 (Fed Cir. 1993)

protein. Thus, *a fortiori*, a description that does not render a claimed invention obvious does not sufficiently describe that invention for purposes of § 112, ¶ 1.

Thus, the court does not view a DNA sequence to be in the possession of an inventor for purposes of the written description requirement even when it is within the rubric of a known protein sequence and the array of codon correspondences defined by the genetic code. Consequently, it is most unlikely the court would consider the infinite population of possible nucleic acid sequences encompassed within the scope of open-ended "comprising" claim constructions to be in the possession of inventors based upon the disclosure of a fragmentary and minor subset of that population.

It should be noted that the above analysis regarding possession of a nucleic acid sequence based upon open-ended "comprising" claim language does not entail consideration of the breadth or nature of the preamble phrase of the claim. In view of the *significance* of the relationship between the transition phrase and the body of the claim (nucleotide or amino acid sequence) in determining the scope of the genus structure, considerations related to the preamble phrase are not controlling. The preoccupation of the interim guidelines with comparative analyses of different preamble phrases at the expense of the considerations enumerated above is misplaced, and makes the interim guidelines seriously deficient.

E) Written Description Considerations Related to EST Claims

EST product claims likely will be expressed in one of two major formats and numerous formats of intermediate scope. Regardless the format, the preamble likely will take multiple forms such as EST, cDNA, cDNA fragment, gene fragment, composition, DNA, DNA fragment, nucleic acid, polynucleotide, or probe. In its simplest form, the narrow scope format will be; "A [preamble phrase] consisting of SEQ ID NO: []." This should represent a species claim falling within the "safe harbor" criteria described under Section C(1) of the interim guidelines, and the written description requirement is satisfied.

The other major format represents a broad scope format. In its simplest form, the broad scope format will be, "A [preamble phrase] comprising SEQ ID NO: []." This represents a genus claim of infinitely broad scope as there is no limitation on the number or sequence of nucleotides that may be added to the 5' or 3' ends of the disclosed SEQ ID NO: [] formula. Clearly, there will be myriad species that are not specifically described in the specification. The scope and level of unpredictability of the structure is so large that the person skilled in the art cannot envisage sufficient species to place the genus in possession of the inventor at the time of filing. The rationale for this conclusion is based upon the examples and discussion developed above regarding application of the "comprising" transition phrase to claims drawn to nucleic acid or amino acid sequences.

Particular attention is directed to EST claims whose patentable utility is predicated upon the capacity of the EST sequence to function as a hybridization probe. Such utilities may

include use of ESTs in forensic identification, tissue type or origin identification, chromosome mapping, chromosome identification, and tagging a gene of known and useful function. Dr. Alberts' communication of June 19, 1997 addressed considerations related to the enablement of such hybridization events. The examples and discussion presented in this response address additional considerations, such as mismatches within a nucleic acid probe, that impart unpredictability to the hybridization process. Specifically, reference is made to Examples A and B from the Training Materials for Enablement and the Sambrook et al. and Wallace et al. articles cited therein. The next article (48) in *Methods in Enzymology*, (Volume 152) after Wallace et al. is by William I. Wood, and is titled, "Gene Cloning Based on Long Oligonucleotide Probes"¹⁰ (copy enclosed). On page 443, Wood states:

[o]nly probes of 17 or longer can be used to screen high-complexity libraries (e.g., a human genomic library). This is because the complexity of the mammalian genome is such that an exact match of any 16-base sequence would be expected at random. When a pool of sequences is used, the number of false positives can be a problem.

This teaching highlights serious problems related to broad EST genus claims reciting "comprising" as the transitional phrase. As indicated previously, such claims include the recited EST sequence corresponding to the SEQUENCE ID NO plus additional nucleic acid sequence attached to either or both ends of the molecule. This additional nucleic acid sequence is of indeterminate length and random sequence composition. Notwithstanding the specificity of the original SEQUENCE ID sequence corresponding to the disclosed EST, Wood teaches that additional overlapping sequences of at least 16 bases would hybridize randomly to regions throughout the genome. Random hybridization leads to false positives, and reduces the predictability of the EST claim structure relative to its disclosed function (utility). This random hybridization problem raises serious questions regarding the enablement of any disclosed utility that relies upon specific hybridization of the disclosed SEQUENCE ID structure.

From the perspective of the written description requirement, proportionately more examples of species sequences must be described in the specification as the size and unpredictability of the EST genus structure increases beyond the specific SEQUENCE ID structure. Since "comprising" transition language supports the introduction of an infinite amount of random sequence, such "comprising" genus claims will require a very large number of described species sequences to demonstrate possession of the claimed genus.

The broad claim breadth discussed above is a function of the "comprising" transitional phrase and the body of the claim. The nature of the preamble phrase has an insignificant effect upon the nature of this claim scope. It is important to acknowledge this distinction regarding the contribution of the preamble phrase, because the interim guidelines are

¹⁰ W. I. Wood, *Methods in Enzymology* 152, 443-447 (1987).

confusing in this regard. The interim guidelines appear to establish a *per se* rule that a genus claim in the format: "DNA, or nucleic acid, or composition comprising SEQUENCE ID NO: []" satisfies the written description requirement, because one skilled in the art can readily envision a sufficient number of members of the claimed genus. This representation regarding envisioning a sufficient number of members is recited to be related to the less specific, generic preamble language. There is no basis in fact or case law for this representation. By contrast, it is at odds with the controlling case law cited in this response. This representation is misleading, and draws attention away from the undue breadth of the genus claims, as well as the claim elements ("comprising" language in conjunction with the SEQUENCE ID NO: formula of the claim body) most responsible for establishing the breadth of the genus claims. In the Final Guidelines, the PTO is requested to address fully the relationship of written description to this claim scope issue. The treatment of this subject must address the relationship of "comprising" transition language to nucleic acid and amino acid sequences expressed as SEQUENCE ID NOs.

Thank you for the opportunity to present the views of the NIH. Please feel free to contact us, if we can be of further assistance.

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Enclosures