

**COMMENTS ON INTERIM GUIDELINES FOR
EXAMINATION UNDER THE 35 U.S.C. §112, FIRST
PARAGRAPH, WRITTEN DESCRIPTION REQUIREMENT**

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Issue 9 of the September 23, 1998, "Request for Comments" is addressed, with a particular view towards inventions in the field of molecular biology in which the informational structure of a nucleotide sequence is altered. This is usually done either to provide a change in the activity of the encoded polypeptide product, protein engineering, or to leave the activity of the encoded product unchanged but realize an improved application of the coding sequence. Since the latter alteration usually requires a very explicit disclosure and rather explicit claims, and the former alteration is the primary area of activity in molecular biology and protein engineering, these comments focus on the effects of the Interim Guidelines on pending applications and allowed-not-yet-issued applications claiming non-naturally occurring nucleotide sequences that may encode altered polypeptide products and/or claiming those altered polypeptide products

A. Nature of docket.

Applications concerning such alterations in the informational structure of a polynucleotide, almost exclusively the choice of codons in a DNA sequence, comprise slightly less than half of my examination docket. In the great majority of applications in this portion of my docket, an adequate written description must also be provided for the changes in the informational structure of the polypeptide product insofar as it recognizes or interacts with molecules that differ from those recognized by the naturally-occurring product, or fails to recognize or interact with molecules ordinarily recognized by - or recognizing - the naturally-occurring product. There are two aspects to providing an adequate written description for such inventions distinct from the treatment provided in the Interim Guidelines, the examples of which concern adequate written descriptions of DNA and RNA polynucleotides recovered in essentially unaltered form: as genomic DNA, as mRNA or tRNA, as an intact or nearly intact cDNA copied enzymatically from a cellular mRNA, or as the fragmentary cDNA termed an Expressed Sequence Tag (EST). The first of these distinct aspects of protein engineering is an adequate written description of the location and nature of the alteration within the coding sequence designed to alter the encoded product. The second is an adequate written description of an alteration that can provide an encoded product with a characteristic that permits it to perform its native function, or an altered function, in a different physical and informational environment.

With regard to altering an encoded product, the Interim Guidelines correctly stress the emphasis of decisions by the Court of Appeals for the Federal Circuit and its predecessor on the adequate disclosure of structural characteristics of a claimed invention as the primary evidence for its possession by an applicant for patent at the time of filing of the application. While nearly every decision cited involves a challenge to priority in an interference proceeding or an attempt to establish continuity of disclosure under 35 U.S.C. §120, the guidelines direct the Examiner to identify the lack of disclosure of a characteristic required for claimed subject matter and establish the burden on that Examiner to show that the specification and the state of the art would not have

5 supplied the missing structural characteristic for one skilled in the relevant art. The evidence that an applicant possessed an invention may be express or conceptual, verbal or graphic, and, for purposes of examination, must include consideration of the level of skill in the art or the knowledge already present in the art of such structure(s). This latter kind of evidence may be crucial in claims to engineered proteins and the polynucleotides that encode them.

B. C(1) analysis for gene product alteration with no, or minimal, functional limitations.

10 Where the invention alters a nucleotide sequence to alter the encoded product, meeting the C(1), or species, component of the guidelines usually commences with disclosure of a prior art nucleotide sequence, or amino acid sequence, and occasionally commences with disclosure of a novel nucleotide sequence. Disclosing the location and nature of each codon change altering either a resulting physical characteristic of the polynucleotide for improved applications in, e.g., a cellular process such as translation, or a resulting change in the amino acid sequence of the encoded product, would complete the C(1) component of the guidelines, each site for change providing a separate subgenus of polynucleotide - due to codon synonymity - and separate species of polypeptide product. Where a native amino acid sequence is member of a genus of polypeptides having a well-characterized three-dimensional structure in solution, e.g., microbial subtilisins, changing a codon to establish a single amino acid change constitutes an adequate written description of an entire genus of partially divergent polypeptide products, all having that specific change at the corresponding location in each. Patents issued from my docket having early effective disclosure dates, e.g. U.S. 5,700,676, in this area of protein engineering have amplified the written description supporting their claims by graphically aligning subtilisin amino acid sequences.

25 Thus, while not contemplated by the Interim Guidelines, completion of the C(1) component for a species, a subgenus, or a genus, of individual, specific codon and amino acid changes need not require the actual disclosure of the native coding sequence or the original nucleotide sequence where the structural characteristics of the claimed invention are defined by the alteration of amino acid sequence of the product as long as the state of the art has long in this area provides the knowledge of codon synonymity and, for many prospective expression hosts, the knowledge of codon utilization preference. The disclosure of the applicant may be combined with the state of the art concerning the particular kind of polypeptide when the Examiner, or a court, seeks to identify structural characteristics of a nucleotide sequence encoding a disclosed, or a prior art, amino acid sequence to be altered, so long as the location of the alteration in the polypeptide's amino acid sequence and the nature of the alteration at that location are adequately described in the specification. Thus the C(1) component under the Interim Guidelines is frequently satisfied by claims that applicants intend to describe specific products bioengineering and the pending applications and allowed applications on this reporter's docket will not be adversely affected.

40 The written description problems that can be encountered in analyzing the C(1) component for the pending applications and allowed applications occur when claims describe encoding polynucleotides and encoded polypeptides that resemble the molecules on a protein-engineering docket, as well as patents issued from such a docket, but lack the disclosure. There are two kinds of claims occurring in applications filed, and patents issued, within the past decade that, by stating a scope that embraces altered polynucleotides encoding polypeptides with altered amino acid sequences, fail to satisfy a C(1) analysis. The percentage similarity claim is premised on the disclosures of a native polynucleotide sequence as the basis for comparison and of a statistical relationship between a single species of starting sequence and a genus of desired divergent sequences. The "modified by one or more amino acid substitutions, deletions or insertions" claim is usually premised on the disclosures of a native polynucleotide sequence as the basis for alteration

and on the statement of the phrase in the specification. In both instances the claims are outside the "safe harbor" of a specific, predictable and iterative, sub-genus or genus of common alterations and/or common locations for alteration. Because such claim limitations describe genera of divergent polynucleotides and polypeptides that are comprehensible to a molecular biologist and a protein engineer and, so long as there are no functional limitations for the encoded product, an examiner can proceed to the C(2) component of the analysis. The Interim Guidelines will only adversely affect such claims in pending and allowed applications on this reporter's docket if their scope exceeds predictability of structure required for the C(2) component of analysis, or if claim limitations require specific function.

C. C(2) analysis for gene product alteration with no, or minimal, functional limitations.

i) percentage identity

A claim describing a polynucleotide encoding a specific amino acid sequence already embraces a broad genus of synonymous coding sequences that may, depending upon the amino acid composition of the encoded product, share as little as 70% identity with a disclosed sequence which is the basis for comparison. The molecular biologist can appreciate the position(s) within each codon where the nucleotide sequence may diverge, the extent of divergence at each position, and generate each of the myriad coding species with a computer program which will also display the location and repertory of available restriction nuclease recognition sites within the nucleotide sequence of each species. This is similar to the example of the 2.75Kb DNA segment discussed in the C(2) analysis component of the Interim Guidelines: the size is constant, the coding capacity does not differ from the polynucleotide isolated or copied from the source organism, and, while the restriction sit map may change, each array is predictable. Most importantly, the encoded product would be identical, easily satisfying the C(2) analysis exemplified in the discussion of the alginate lyase in the Interim Guidelines. Anyone in the arts of molecular biology and protein engineering would be in constructive possession of the claimed invention upon reading the specification, just as the applicant had been when it was filed.

A claim describing a polynucleotide encoding an amino acid sequence sharing 70% identity with the amino acid sequence encoded by a disclosed polynucleotide sequence which is the basis for comparison will, however, embrace a far broader genus. A claim describing 70% similarity, often loosely referred to as "homology", defines a far broader scope which depends upon the association matrix chosen for application in the algorithm which definitely sets the scope. In the case of 70% amino acid sequence identity, a series of genera exist: one in fact, for each instance of a single substituted, deleted, or inserted amino acid by comparison with the reference amino acid sequence encoded by the polynucleotide disclosed in the specification and one for each member of the successive sets of such alterations. The average codon permutation per amino acid is less than three but the number of amino acid permutations for each location in the reference amino acid sequence - including no change - is twenty-two. The degree of structural conservation shared with the reference polynucleotide by some species embraced by such a claim may fall to almost 45% (0.66×0.70), the regions where conservation is shared will not be constant, and, since insertions and deletions are among the permutations, the size may vary two fold ($130/70$). It is not clear that such subject matter can be considered to be supported by an adequate written description under the C(2) component of the guidelines, even if a computational program provided all of the alternative sequences, where all of the identifying characteristics discussed for the 2.57 Kb DNA exemplified in the C(2) analysis of the Interim Guidelines will vary independently of each other.

If a functional limitation is recited in the claim for the encoded polypeptide, even the requirement that it retain its native activity, a C(2) analysis under the Interim Guidelines will fall to

determine that an adequate written description has provided. Unless the encoded gene product is a member of a thoroughly-characterized genus of proteins, such as the subtilisins, no way has yet been devised to predict the result on the structure of the encoded product of such extensive substitutions: retention of the kinds of characteristics exemplified in the discussion of the alginate lyase in the Interim Guidelines cannot be predicted. Subtilisins have so far sustained only 5% simultaneous amino acid sequence alteration without losing their basic function and if a claim described a polynucleotide encoding an amino acid sequence sharing 95% identity with the amino acid sequence encoded by a disclosed polynucleotide sequence which is the basis for comparison, it is possible that a Declaration under 37 CFR 1.132 addressing a rejection for lack of an adequate written description might be successful in establishing possession by an applicant of a claimed, isofunctional, invention at the time the application was filed.

Setting forth a series of specific amino acid permutations, e.g., by stating a formula and combining it with a series of disclosed species exemplifying the breadth of structural diversity desired in a claim as is characteristic in the peptide design arts, see U.S. Patent 5, 804,558, will establish an adequate written description supporting the claims. The greater the size of the polypeptide however, the greater the need for simplifying structural components, an approach commonly employed in specifications describing altered plasma proteins such as tissue plasminogen activator variants where the domains are defined and a series of alterations within each domain are then defined together with domain deletions, substitutions or additions. See the parallel discussion of enablement for structural alterations in Genentech, Inc. v. The Wellcome Foundation Ltd., 29 F.3d 1555, 1564-65, 31 USPQ2d 1161, 1168 (Fed. Cir. 1994). Absent a basis in the application for defining their predictable structural features, claims to altered polynucleotide and polypeptide in pending and allowed applications on this reporter's docket having a scope defined primarily by statistical relationship to a reference structure can be adversely affected by the Interim Guidelines.

ii) "modified by one or more amino acid substitutions, deletions or insertions".

This alternative claim format is more amenable to a favorable C(2) component analysis, even with a functional limitation requiring retention of native function. The scope of structural alteration can be interpreted by an Examiner as *de minimis* and a number of examples exist in the art of protein engineering where, with native amino acid sequences as the basis for comparison, the underlying polynucleotide coding sequences were altered to add terminal peptide regions, delete terminal peptide regions and, in a few instances, insert internal peptide regions without reference to a previously determined three-dimensional structure. In these last instances, however, amino acid sequence feature conservation in a genus of related proteins was an important factor in predicting the continued function of the altered protein. While more an approach to resolving *de minimis* enablement issues than written description issues, alanine scanning mutagenesis has, since the mid-1980's, been used to probe, by replacing the codon specifying a native amino acid with a codon specifying alanine at successive locations in the nucleotide sequence encoding a polypeptide, the functionality of regions in a known amino acid sequence. No prior knowledge of the three-dimensional structure of a polypeptide and no, or very little, prior information gained by sequence alignment of an applicant's novel amino acid sequence with known, prior art amino acid sequences, were required to locate positions safe for alanine substitutions. A verbal description of this or similar techniques in an effort to establish a constructive possession of a polynucleotide modified by one or more standard amino acid sequence modifications without an actual disclosure of the altered polynucleotide and/or polypeptide species is unlikely to be challenged during examination in view of the Interim Guidelines because the structure of the altered products is largely unchanged and the nature of the change is specific and the incidence limited. Attempts to enforce a claim with such a recitation in an interference, or in court, against another who has modified the DNA

and the polypeptide that an issued patent actually, rather than constructively, discloses, may fail if the opposing argument is premised on the lack of an adequate written description of the infringing or interfering product(s) where they were designed to specifically alter the activity of the native polypeptide product in a fashion not suggested by the patentee's specification. Even in the absence of a basis in the application for defining their predictable structural features, claims to altered polynucleotides and polypeptides in pending and allowed applications on this reporter's docket having a scope defined primarily by generic alterations at unspecified locations in their sequences may only be adversely affected by the Interim Guidelines in attempts at enforcement.

10 D. The C(1) analysis for gene product alteration linked to functional alteration *in vivo* must be satisfied.

The written description for a claimed, modified, product with a modified function resulting from its modified structure is similar to that for any other altered organic compound so long as the modified function is exhibited in an industrial or extracellular environment. Here, satisfying the same description requirements to be met in defining a chemical species will clearly satisfy the C(1) component of the analysis under the Interim Guidelines. The molecular biologist and protein engineer can thus know the location of the alteration in the structure of the nucleotide and/or amino acid sequence, the generic nature of the alteration(s) that may be performed, and which species of substituents to use - if a substitution is comprised among the alterations - to provide the claimed functionality. Where the native polypeptide to be altered is characterized well enough in the art, or by the specification, so that the sites for the same modifications in its counterparts from other natural sources can be identified, there will be ample evidence of a constructive, adequate, written disclosure of a genus of such heterofunctional products.

25 An aspect of unpredictability in structural relationships not contemplated by the Interim Guidelines arises where a product having an altered functionality is described by a claim limitation as enhancing, suppressing, or otherwise effecting an intracellular process or an intercellular process. If the desired effect is only proposed in the specification, and not exemplified in a cell or organism providing an environment characteristic of that in which the altered product would exert its desired effect, the Interim Guidelines might be construed as requiring a demonstration that the structural modification described by the claim and the cellular or organism has the effect described by the claim and is compatible with the larger structure, the cell or organism, wherein the claimed function is intended. This is particularly the case if definitional statements in the specification require that the claim terms be construed as describing a measurable effect exerted by the product, establishing that the uncertain, constructive, possession of the claimed invention was an actual, predictable, possession. In the absence of definitional statements requiring an effect, it is possible that an inherent limitation that the modified product compete effectively within the cell or organism to dominate the effects of other, native, cellular products may be considered to be present in claims describing such altered products.

45 Since the Interim Guidelines do not address this issue, and only one instance of claimed subject matter describing an altered product proposed to have specific intracellular function was encountered by this reporter since the publication of the guidelines, the results may be of interest. No rejection for lack of an adequate written description was stated because the applicant's altered product closely structurally resembled products altered by Nature - naturally-arising allelic variants described in the prior art - that clearly had measurable heterofunctional effects in the cells of the unfortunate individuals in which they were expressed. The applicant's disclosed embodiment functioned *in vitro* and the applicant proposed iteration of its specific, modified, structural

feature(s) to increase its interaction with a specific, designated, cellular structure and such iteration could clearly be performed. This indicated that the applicant possessed the concept of those features that could sufficiently distinguish the claimed invention, both structurally and functionally, from other generic or native molecules of the same class and further indicated that the
5 specification would convey that possession to the molecular biologist and protein engineer. Unless the discussion of the Interim Guidelines is extended to address the informational nature of nucleic acid sequences and amino acid sequences as well as their strictly chemical nature, analysis of the presence or absence of an adequate written description of modified cellular effector polypeptides must be performed on an *ad hoc* basis if the C(1) analysis component is satisfied.

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E. Reaching a C(2) analysis component for gene product alteration linked to functional alteration is inappropriate.

15 While one need not know why an invention works as it does in order to establish its patentability, if a specific structure and a specific kind of modification to that structure are not described by the specification, or by the specification taken together with the prior art, such that the molecular biologist or protein engineer cannot see the basis for the interaction with cellular structures that provides the effect described by functional limitation(s) of the claimed invention, it is not clear that the C(2) analysis component is appropriately invoked. In this instance the deposit requirement for biological materials relevant to enablement is also relevant to possession of the
20 claimed invention at least as of the date of deposit. This is because the kind of external, resultant, characteristics set forth in the discussion of the naturally-occurring alginate lyase in the Interim Guidelines cannot inform one practicing the relevant arts that the applicant knows the nature of a claimed invention where some structural change was made - as in chemical mutagenesis procedures - and some altered function observed, if only at the level of a change in phenotype. It is the unique nature of inventions in the area of molecular biology, however, that the structural modifications to a nucleotide coding sequence can, with DNA sequencing to compare the altered allele with a native allele can be determined, the resulting structural change in the amino acid sequence deduced, and screening of effects of the product on cellular growth and differentiation
25 conducted to determine the cellular mechanisms that it affects. While none of this can be conveyed by an applicant in writing at the first observation, the cell possessing the altered allele and altered expression product can be deposited and a preliminary or provisional filing made. The date of both the possession of the DNA sequence and the determination of the nature of the distinguishing characteristic(s) that result in an effect of the product recited in a functional claim
30 limitation of altered activity is the date of the possession of a species the claimed invention that is a DNA sequence and amino acid sequence. Fiers v. Revel v. Sugano, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993).

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