Comment 44 NIH/Jack Spiegel

March 22, 2000

The Honorable Q. Todd Dickinson
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks
Box 8
Patent and Trademark Office
Washington D.C. 20231

Attention: Mark Nagumo; Steven Walsh, and Linda Therkorn

Dear Commissioner Dickinson:

The written remarks presented herein relate to the request for comments on the Interim Utility Guidelines and the request for comments on the Interim Written Description Guidelines. Both requests were announced in the Federal Register December 21, 1999. The remarks respond also to the released Training Materials associated with each respective interim guideline.

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 further 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).

Introduction and Background to Federal Transfer of Biotechnology:

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 FTTA provides incentives comprising cash awards and distribution of a portion of licensing royalties back to the laboratory and inventors.

NIH Advancement of the 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 1,100 issued patents, executed over 1,500 license agreements, generated over 250 million dollars in royalties, and entered into over 500 Cooperative Research and Development Awards (CRADAs). While significant, these activities reflect the 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 85% of the 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, the NIH is a major stakeholder in the genomic arena, and the NIH has commensurate interest in any proposed guidelines related to the examination and patentability of biomedical inventions describing nucleic acid and amino acid sequences.

I Comments on the Revised Interim Utility Examination Guidelines

Revisions to the Utility Guidelines are proposed to address comments received regarding patentability issues associated with claims to certain DNA sequences, including Expressed Sequence Tags (ESTs). Toward this end, the Revised Interim Utility Guidelines expand the prior guidelines to encompass consideration of whether an asserted credible utility is also specific and substantial. Additionally, a new Example 10, "DNA Fragment Full Open Reading Frame (ORF)", is included in the training materials accompanying the guidelines. The NIH commends the PTO on the expanded three-prong test proposed for utility, and the commitment to apply this standard to claims drawn to DNA sequences. The NIH submits for consideration the following comments directed to the methodology and the new training materials.

A) Comments on Methodology

(1) Establishing a Complete Prosecution Record

The NIH wishes to raise two issues related to the newly proposed guideline methodology. The first issue concerns creating a more complete official record when a determination of well-established utility is made. When a well-established utility is deemed to exist, the examiner is directed not to make a utility rejection regardless of any assertions made or not made by applicant. Each example in the training materials definitively illustrates this determination as part of the utility analysis. However, what is missing from the guideline methodology itself or the accompanying examples is the instruction or expectation that an affirmation of the well-established utility be memorialized in the official record.

It is important that the record be clear regarding the disposition of all elements of patentability. This is particularly so in a case, as here, where the determination of well-established utility includes considerations beyond those disclosed in the specification or applicant's submissions, which otherwise do not become part of the prosecution history. Furthermore, it is important to distinguish whether the examiner accepted a utility asserted by applicant, or relied upon a well-established utility after dismissing asserted utilities. In a controversial area such as the utility of gene/gene fragment patents, silence is not golden. This potentially important oversight can be easily remedied by instructions in the guideline methodology or in the training materials to memorialize any independent determination of well-established utility in the prosecution history.

(2) *Prima Facie* Case For No Well-Established Utility: Proving a Negative

The second issue with the methodology also concerns the determination of a well-established utility, and is set forth in Section 3(b). This section relates to a situation when no specific and substantial utility is disclosed or known, and presumably there is no art of record establishing a well-established utility. The examiner is required to set forth a *prima facie* case that it is more likely than not that a person skilled in the art would not be aware of any well-established credible utility. This *prima facie* case requires factual showings analogous to those required to establish that an asserted specific and substantial utility is not credible. This provision appears to require the examiner to prove a negative; i.e., what persons skilled in the art do not know. Indeed, the examples in the Training Materials merely show the examiner indicating that the art of record does not disclose or suggest a well-established utility for the invention. It is recommended that a statement that no well-established utility is of record should be sufficient, and this particular *prima facie* requirement be removed from the guideline methodology.

B) Comments on Training Materials

(1) Generic Utilities for ESTs

The new interim guidelines to highlight the specific and substantial requirements for utility are well served by this modification. In this regard, the NIH appreciates the objective to keep the guideline methodology simple and applicable to all types of inventions. However, this focuses a heightened obligation upon the Training Materials to educate and instruct the examining corps about specific utility issues and resolutions that have evolved over three years of discourse since the PTO first announced that ESTs were patentable based upon their utility as probes. One criticism by the NIH is that the new Training Materials accompanying the Revised Interim Utility Guidelines do not communicate the important issues resolved during this period of debate with sufficient prominence and emphasis.

The chronology of the interactions regarding this subject includes the April 2, 1997 correspondence from Commissioner Lehman to the Director of the NIH confirming our analysis negating the adequacy of a utility of ESTs as probes for genes of unknown function. However, the Commissioner opined that other general uses of ESTs such as for forensic identification, tissue type or origin identification, chromosome mapping, and chromosome identification could satisfy the requirement. The PTO advanced this interpretation of EST utility in various public forums for nearly three years, including issuing EST patents based upon such utilities.

Following much formal and informal discourse on the subject, the Commissioner and his staff discussed several significant position shifts relative to utility issues at a December 1999 meeting held at the NIH. The PTO previewed major points of the then upcoming Interim Utility Guidelines, and discussed utility issues in the context of three generations of gene sequence applications being examined at the PTO. The first generation was identified as including typical anonymous EST sequences that rely upon assertions of general utilities. The PTO indicated that such generalized utilities characteristic of first generation EST applications would be subject to rejection as lacking a specific and/or substantial asserted utility.

The NIH supports this substantive reevaluation of EST utility, and formally expressed its appreciation in a communication to Commissioner Dickinson dated December 21, 1999. The NIH, however, is surprised and disappointed that the new Training Materials do not address more prominently these resolved EST utility issues in light of the expressed goal of the Interim Utility Guidelines. This is illustrated by Example 9 being the only training example drawn to ESTs. Example 9 of the new Training Materials is substantially the same as in the original Utility Guideline materials. It addresses an issue which has not been a subject of controversy or confusion since the above-mentioned April 2, 1997 communication (i.e., ESTs only disclosed as a probe for unknown genes is not a sufficient patentable utility). By contrast, significant issues regarding generalized use of EST probes for chromosome mapping, tissue type or origin identification, forensic identification or diagnostic markers are relegated to less prominent treatment within the "Synopsis of Application of the Revised Interim Utility Guidelines" preceding the actual Utility Guidelines Training Examples. Indeed, an examiner may have to analyze this section carefully to come away with more than the impression that these are utilities whose credibility should not be questioned.

The corps examining large numbers of EST claims is burdened with a long history of contradictory statements surrounding this controversial issue in the biotechnology community. The NIH believes it is prudent that this issue of general non-specific and/or non-substantial utility relative to EST sequences be expressly addressed and more clearly analyzed in appropriate detailed examples within the Training Materials.

(2) Theoretical Utilities Based on Sequence Homology / Example 10

New Example 10 in the Interim Utility Guidelines Training Materials relates to the so called "second generation" of nucleic acid sequence applications being examined by the PTO. These are applications that disclose at least one open reading frame (ORF) plus a theoretical characterization of the corresponding protein based on homology to other known proteins. There is no actual data or analysis to establish a specific biological property, activity, or function for the expressed protein. The utility test proposed by the PTO for second generation sequences asks if sequence homology is sufficient to provide reasonable confidence that the protein encoded by the ORF would have a well-established function. The NIH does not believe this is the proper standard for determining utility in this art. Guiding legal authority on the issue of specific utility based on homologous structures in the art is found in *Brenner v. Manson,* 148 USPQ 689 (SCT 1966). This is the seminal Supreme Court decision on the legal requirement that a utility be specific and substantial in addition to being credible.

(a) Direction from the Court Regarding Specific Utility

Brenner v. Manson

Manson's invention involved a method for making a known steroid. The PTO asserted the steroid compound in question (i.e., the product made by the claimed method) had no known utility and, therefore, the method of making it was not useful under the patent statute. The Court affirmed this concept. This is the fundamental precept underlying Example 9 of the Training Materials.

Manson argued that the steroid compound did have utility because an adjacent homologue had been shown in the art to have a tumor-inhibiting effect in mice. Adjacent homologues in chemical practice are considered to be sufficiently similar structurally to infer a common or similar function. This is the accepted basis for establishing a *prima facie* case of obviousness between adjacent homologues.

The Court looked to the level of skill and predictability in the steroid art. The Court found evidence for a heightened unpredictability of compounds in this field. It was accepted in this art that minor changes in the structure of a steroid were able to produce profound changes in its biological activity. Based upon that level of unpredictability in the art, the Court ruled that inference of similar function from homologous compounds was by itself insufficient for purposes of demonstrating a specific and substantial utility. In order to assert the invention had a specific utility, the Court required Manson to actually demonstrate it. Manson had to show that his steroids possessed tumor-inhibiting properties before he could support the credibility of this asserted utility through reliance on homologous prior art. Beyond considering only technical matters reflecting the state of knowledge and predictability in the art, the Court looks to the larger public policy issues underlying their decision. The Court concluded that a rigorous standard of specific and substantial requirements for utility was necessary to maintain the *quid pro quo* foundation on which the patent grant rests. The Court stated at page 695:

> The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form - there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

It appears, therefore, that *Brenner v. Manson* is controlling case law for fact patterns asserting specific and substantial utility based solely on homology in an unpredictable art. In order to assess how *Brenner v. Manson* should be applied to utility issues associated with "Second Generation" DNA sequences, one needs to address two inquiries. First, does other case law exist that may modify or refine *Brenner v. Manson*? Second, what is the level of unpredictability in the DNA sequence art?

Other Court Decisions:

In his January 7, 2000 letter to Drs. Varmus and Collins, Commissioner Dickinson referenced two case citations in addition to *Brenner v.Manson*, as providing guidance in applying the utility requirement on a case by case basis. These court decisions are *In re Folkers,* and *In re Brana*. The context of that portion of the Commissioner's comments involved responding to NIH concerns voiced in a preceding December 21, 1999 letter regarding the specific utility of DNA sequences in "Second Generation" sequences (i.e., specific utility supported solely by a theoretical characterization of protein function derived from homology data). *In re Folkers,* 145 USPQ 390,393 (CCPA 1965) was cited for the proposition that some uses can be immediately inferred from a recital of certain properties. *In re Brana,* 34 USPQ2d 1436,1441 (Fed. Cir. 1995) was cited for its teaching that evidence of success in structurally similar compounds can be relevant in determining whether one skilled in the art would believe an asserted utility. Finally, the Supreme Court decision *Brenner v. Manson*, was cited, as described above, for its teaching that despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics. The NIH submits that these cases actually provide a unified and consistent legal framework upon which to evaluate the utility of "second generation" sequences.

In re Folkers

The fact pattern and decision in *In re Folkers* supports the principles and standards set forth in *Brenner v. Manson*. In *In re Folkers,* the CCPA ruled that it was uncontroverted that Folkers had invented compounds that were quinones and hydroquinones. Also unchallenged was the assertion that quinone and hydroquinone compounds possess electron transport activity. This structure-function relationship was considered predictable and accepted in the art. It is at this point that Folkers' compounds succeed, where Manson's steroid failed. The difference in predictability in the respective arts permitted Folkers to assert that his compounds possessed a particular functional property, but denied that opportunity to Manson. Once it was established that Folkers compounds possessed an accepted property (electron transport), it then became appropriate to ask if there are well-established utilities known in the art associated with the electron transport property in this class of compounds. While the outcomes of *In re Folkers* and *Brenner v. Manson* are opposite, the methodologies pursued and the application of law in both cases are both consistent. Indeed, at page 696 of *Brenner v. Manson*, the Court commented on how the decisions of the CCPA were in accord with their decision process in this matter. One of the CCPA cases cited reflecting this accord is *In re Folkers*.

In re Brana

The fact pattern of *In re Brana* also supports the principles and standards set out in *Brenner v. Manson*. Here, Brana disclosed 5-nitrobenzo[de]isoquinoline-1,3-dione compounds for use as anti-tumor substances. Brana employed *in vitro* and *in vivo* mouse model systems to test the anti-tumor activity of his compounds, and he compared his compounds to others known in the art to have this property. Brana found his compounds superior in these comparative tests. The utility challenges overcome by Brana were twofold. First, the test systems employed by Brana

were challenged as to whether they were specific for the asserted utility. The second challenge was to the credibility of the asserted utility based upon those tests.

The CAFC found the test systems used by Brana appropriate and sufficient to support the specific anti-tumor property (utility) asserted for their compounds. Unlike the fact pattern in *In re Folkers*, the level of predictability in this art did not permit Brana to infer an anti-tumor property based only on the structure of his compounds. Consequently, Brana relied upon experimental evidence to assert that specific anti-tumor property. This empirical showing of specific utility distinguished this fact pattern from *Brenner v. Manson*. Had Brana attempted to rely solely on evidence from structurally similar compounds in the art to assert possession of a specific anti-tumor utility by his compounds, that assertion would have been subject to rejection under the *Brenner v. Manson* principle.

The second challenge in *In re Brana* involved the credibility of the asserted utility. Once the CAFC ruled the utility was specific and substantial, their analysis turned to how one skilled in the art would view the credibility of the asserted utility. It was in that context that the Court indicated that evidence from the prior art regarding structurally similar compounds is relevant in determining whether one skilled in art would believe (i.e., find credible) an otherwise specific and substantial utility. This is analogous to looking to homologous prior art for a well-established utility associated with a specific property of the invention. Such specific properties require substantiation by empirical showing in unpredictable arts, but can be inferred from the disclosed structure in predictable arts (e.g., *In re Folkers*). Evidence regarding structurally similar compounds from the prior art was not used to establish the specific anti-tumor property of the Brana compounds; Brana did that through experimentation on his compounds.

It is clear, therefore, that *In re Folkers* and *In re Brana* are in accord with *Brenner v. Manson* regarding the basis for determining a specific property or utility associated with a chemical compound. Both decisions advance *Brenner v. Manson* by describing appropriate use of homologous art to provide credible support or a well-established utility for a specific property or use associated with the claimed invention.

The fact pattern in *Brenner v. Manson* required that there by unpredictability in the art in order to negate otherwise controlling principles linking structure and function in closely related homologues. It is necessary, therefore, to examine the level of unpredictability in the genomics art in order to access if the fact pattern of *Brenner v. Manson* controls in the class of "Second Generation" sequences with asserted theoretical utility based upon homology to prior art sequences.

(b) Level of Skill and Predictability of the Art

(i) General Considerations

The DNA and protein arts are recognized as unpredictable, such that minor changes in the nucleotide or amino acid sequences of these molecules may produce profound changes in biological activity. A classic example of this is sickle cell anemia arising from a single amino acid substitution of valine for glutamic acid as the sixth amino acid in the beta chain of

hemoglobin A. Genomic sequences display some elements of conservation of sequence among individuals and taxonomic species. However, genetic and protein sequences are characterized by a marked degree of variation or polymorphism. In almost all cases one is not able to predict the functional significance of particular sequence polymorphisms. The direction of the CAFC over the past nine years has been to recognize this unpredictability in the DNA art, and to require gene-related molecules be defined by their sequences and/or other distinguishing physical properties. In this regard, the direction of the courts has been to treat DNA and protein structures as chemicals.

Despite this direction from the courts, this art has not yet been able to decipher predictable and workable relationships between DNA/protein sequence polymorphism and functional activity. The biotechnology community has not been able to establish a workable counterpart to structural homology (structural obviousness), whereby a measure of sequence similarity is recognized in the art to imply a reasonable expectation of functional equivalence. Many factors contribute to the unpredictability of this art. Fore example, it is important, when evaluating the potential effect of mismatches, to know if they are randomly distributed through the protein, clustered in one or more domains, or if mismatches are located/concentrated in known critical areas of the molecule; e.g., at the active site. At best, sequence similarity/homology data provides the person skilled in this art a starting point to hypothesize potential biological function. The confidence level afforded by such scientific first cuts falls far short of the *Brenner v. Manson* standard for asserting a specific utility for patent purposes. In this art, establishing the function of a gene sequence still requires expression of the gene, and empirical characterization of the protein product.

Beyond the unpredictability that exists in establishing a structure-biological function relationship for simple DNA sequences, the art is recognizing increasingly that many genes share sequence homology relationship within large and markedly heterogeneous families. A partial list of well known gene families include kinases, membrane-associated proteins, helicases, zinc fingers, and traffic ATPases. These homology families encompass proteins that may share certain structural domains, but are associated with a variety of different biological functions. Determining specific utility in such diverse families requires distinguishing the particular structure/function relationship of the claimed family member from the array of different utilities exhibited by divergent members of the family. For example, membrane-associated receptors may be categorized as members of the same homologous family based upon sequence similarities in their transmembrane domains. Well-established biological functions associated with individual family members, however, arise from specific properties associated with their extracellular binding domains. Clearly, it is not appropriate to ascribe specific utilities associated with one family member to others with different binding domains. To afford specific utility based on shared homology to the transmembrane domain is to encourage patents that provide the public no more utility than it already possessed from knowledge of the broad subject class. This does not satisfy the *quid pro quo* of the patent grant and, therefore, fails the specific utility standard required by *Brenner v. Manson*.

(ii) Example 10-Specific Comments

Example 10 of the Training Materials illustrates a "Second Generation" invention where a sequenced ORF was asserted to be a DNA ligase based upon a 95% similarity score of amino acid homology. The previously discussed considerations of unpredictability in this art apply even at this apparently high level of similarity. For example, it may be critically important in order to be able to assert an enzyme property to the sequence to have information regarding the number and position of mismatches.

A fundamental flaw in the analysis of Example 10, however, is the conclusion that "[b]ased upon applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID NO:2 encodes a DNA ligase." This is flawed because there is no evidence provided in Example 10 that the DNA ligase art is more predictable than the general DNA/protein art in the ability to identify protein activity through sequence homology. In fact, there is no evidence in Example 10 that the state of art was considered. Consequently, there is no basis in Example 10 to presume that a person skilled in this art would accept the stated assumption in the absence of experimental evidence demonstrating the protein of SEQ ID NO: 2 actually displayed DNA ligase activity.

The flawed logic of Example 10 is illustrated vividly if the fact pattern is modified to assume that the art was not yet aware of the DNA/protein sequences of DNA ligase. This is not unreasonable since only a fraction of the genes/proteins have been cloned/isolated and sequenced. Example 10 teaches that the next highest level of homology found in the art was a 50% match to alpha-actin. Since the DNA/amino acid sequences of DNA ligases would not be in the searchable databases, would that 50% homology support an assertion by applicant that the protein was instead alpha-actin? Granting patents based upon the highest known homology at the time of filing undermines confidence in the patent system by giving an already unpredictable art the appearance of a patent guessing game.

The Supreme Court in *Brenner v. Manson* demonstrated foresight in identifying specific and substantial utility as a critical component to the patent *quid pro quo*. The Court provided meaning to the criticality of utility by requiring the specific and substantial aspect to be rigorously applied. The Court secured that rigorous application by looking to the level of skill in the art for guidance. When that level of skill is unpredictable, specific and substantial utility is protected by preventing applicant from extrapolating it from homologous prior art. That inability to extrapolate from homologous prior art extends to adjacent homologues, the closest homology known in chemical practice.

Conclusion

The PTO has diligently sought the sense of those skilled in this art regarding patenting of gene sequences. The NIH has been formally communicating with the PTO regarding these issues since March 1997. Much formal debate regarding written description and utility requirements related to gene sequences has occurred since the first Interim Written Description Guidelines were published for comment back in June 1998. The PTO has heard from Nobel Laureates, the Director of the Human Genome Project, the National Academy of Sciences, the Association of American Medical Colleges, academic scholars, and representatives of industry. Each cautioned against granting broad patents on gene sequences (particularly sequence fragments) based upon asserted general and theoretical utilities that are not considered specific and substantial utilities.

Through these cautions, each provided a sense of the unpredictable nature of this art. This constituency earnestly values its piece of the *quid pro quo* for its importance to the advancement of scientific research and discovery, the public health, and commercial development in the biotechnology/pharmaceutical industry.

A perception has arisen that the NIH and others in the scientific community seek to establish a new standard of the utility for gene sequence applications. Some view the NIH as advocating a radical standard that is extraordinarily high compared to technologies in other arts, and one that does not comport with historical practice. The remedy for our concern, however, lies not in a revolutionary new-order utility, but in the landmark *Brenner v. Manson* Supreme Court decision, which defines the modern concept of specific and substantial utility. The fact pattern of this case focuses on a method of making a product, where the ultimate consideration requires that the final product demonstrate a specific, substantial, and credible utility. The asserted utility of the final product is based upon structural homology in an unpredictable art. This is a case whose conclusion of law follows from the realization that homology in an unpredictable art cannot, by itself, provide a specific utility.

The PTO is the steward of the patent laws. That responsibility includes stewardship of the American public's interest in the *quid pro quo* of the patents it issues. The Supreme Court clearly articulated the specific and substantial utility standard and its relation to that *quid pro quo* in a fact pattern analogous to "Second Generation" sequence applications. Consequently, the fact pattern set forth in *Brenner v. Manson* is not met by a patent applicant's mere assertion of any specific and substantial utility for DNA/protein sequences based solely on homology to prior art sequences as currently proposed in the analysis of Example 10. It is respectfully requested that the PTO revise Example 10 of the Interim Utility Guideline Training Materials corresponding to examination of "Second Generation" sequences to be in concert with this controlling case law.

II Comments on the Revised Interim Written Description Guidelines

The Interim Written Description Guideline methodology was revised to be technology neutral, and to include considerations related to new/amended claims, process claims, and product by process claims. The NIH commends the PTO on these improvements to the methodology. The NIH commends the PTO also on Example 7 in theTraining Materials accompanying the guidelines, which is drawn to an EST claimed as "[a]n isolated DNA comprising SEQ ID NO: 16". This example recites:

> Here, the specification discloses only a single common structural feature shared by members of the claimed genus, i.e., SEQ ID NO: 16. Since the claimed genus encompasses genes yet to be discovered, DNA constructs that encode fusion proteins, etc., the disclosed structural feature does not "constitute a substantial portion" of the claimed genus. Therefore, the disclosure of SEQ ID NO: 16 does not provide an adequate description of the claimed genus.

This understanding that a DNA sequence fragment claimed with open transition language does not put one in possession of larger DNA molecules, including full-length cDNAs or genes, relieves a significant concern raised by the NIH and others in the biotechnology research and development community. While the conclusion drawn from Example 7 is explicit, the NIH believes the Guidelines and supporting Training Materials would benefit from a clearer and fuller development of the meaning and effect of open transition language and intermediate transition language (i.e., consisting essentially of) in DNA and protein sequence claims. The NIH respectfully submits for consideration the following comments and suggestions to achieve that goal.

A) Considerations Regarding Open Transition Language

The guidelines indicate that the entire claim must be considered, including the preamble language and the transitional phrase. Reference is drawn to endnote 27 to clarify and define the meaning of certain transition terms. "Comprising" is defined according to its general claim drafting meaning as covering the expressly recited subject matter, alone or in combination with unrecited subject matter. In responses addressing comments from the prior Interim Guidelines and in various examples, open transition language is taken to further encompass molecules extended without limit at the 3' or 5' ends of DNA and at the amino or carboxy termini of proteins. It is suggested that this important caveat associated with DNA and protein claims be addressed specifically with appropriate case law citations supporting this distinction, including how this relates to the polymer art (e.g., *Genentech v. Chiron, 42 USPQ2d 1608 (Fed Cir. 1997)* and *In re Baxter, 210 USPQ 795 (CCPA 1981)).*

Attention is directed to the response to Comment 35, where the PTO indicated the following:

> Although an applicant presenting an original claim to an EST using open-ended claim language with disclosure of only the EST sequence is not in possession of any arbitrary specific possible molecule that contains the EST, the applicant may be in possession of a broad genus of DNA where the EST is in any random nucleic acid sequence.

This statement does not appear consistent with the conclusion reached in Example 7 of the Training materials. The statement, moreover, is troublesome on a basal level.
As enumerated in Section 1 of the guidelines, written description conveys that the inventor was in possession of the claimed invention at the time of filing. Therefore, according to the above statement, the inventor is in possession of all DNA molecules with random sequences containing the EST as a sub-component. Since DNA sequence is not punctuated, unique (non-repetitive) sequence appears random until a subset is identified that encodes a specific function, e.g., a protein. In the scenario above, when a post-filing function is discovered for the sequence, i.e., the sequence ceases to be random, does the patentee cease being in possession since it now is a specific (particular) molecule that includes the EST sequence? Clearly, the above statement cries out for further clarification.

Another confusing situation relates to a comparison of Examples 7 and 8. As described previously, Example 7 relates to an EST claim employing open transitional language that does

not satisfy the written description requirement. At the end of the example, however, is a caveat stating, "[i]n situations where the specification indicates that the SEQ ID NO: is a full-length cDNA open reading frame and the claim **cannot** read on a gene, the claimed invention would meet the written description requirement." Example 8 is drawn to an open reading frame sequence claimed in analogous open transitional language. The example concludes that the DNA encodes a DNA ligase, and that the written description requirement is satisfied. It is not clear why the caveat at the end of Example 7 does not apply.

Example 8 is indicative of the excessive breadth that derives from the claim format where a term such "nucleic acid" or "DNA" is the preamble, "comprising" is the transitional term, and the body of the claim consists of a SEQ ID NO:. As indicated in Example 8, this format reads on many different categories or classes of molecules far outside the physical parameters or properties of the molecule represented by the SEQ ID NO:, including fusion proteins, vectors, etc. While this generally is considered a scope issue under the enablement provision of Section 112, it also constitutes a problem under written description.

This claim format has been characterized by means of several variations on a similar theme. One way describes a genus of nucleic acids or DNA molecules encompassing the SEQ ID NO:, where that SEQ ID NO: represents a species. Another format describes the nucleic acid molecules as a genus of combinations, where the SEQ ID NO: is a sub-combination element. A variation on the combination/sub-combination concept views the SEQ ID NO: as an intermediate that becomes part of a genus of larger final products. Regardless the characterization, this claim format must satisfy the premise that the basic SEQ ID NO: disclosure puts one in possession of the genus, combination, or the larger final product. The NIH submits that disclosure of an intermediate structure alone does not support possession (i.e., an adequate written description) of a larger final product structure. Similarly, disclosure of a sub-combination structure alone does not support possession a larger combination structure. In each case, the identity, structure, characteristics, and properties of the larger final product or the combination structure is not known. The genus-species relationship provides the same issues. Since additional residues are added to the ends of DNA structure, the genus of nucleic acids envisaged represent larger physical structures (sequences) than the SEQ ID NO: species. With the possible exception of polymerization of a defined subunit, it is not clear how a single smaller structure puts one in possession of many larger structures.

It is important to remember that the chemical structure represented by the SEQ ID NO: loses its structural integrity when its ends are extended through addition of additional residues. This is very different from mechanical practice where the combination and sub-combination of elements maintain their physical integrity. This is relevant also to when "comprising" language is characterized as creating as a genus – species relationship. The disclosed molecule that represents the species looses its distinct chemical identity as it is converted into larger molecules with addition of terminal residues.

In view of these comments, we request the PTO revisit Example 8 from the perspective of better defining how there can be possession of molecules with physical properties and sequence structure disparate from those of the disclosed sequence. It is requested that the PTO evaluate this issue of sub-combination structures providing written description support for significantly

larger combination compounds with unknown properties and structure from the perspective of *In re Papesch, 137 USPQ (CCPA 1963)* that teaches a chemical compound and its properties are inseparable. Therefore, a formula (e.g., a DNA sequence) is not the compound; nor is the formula what is patented.

In chemical practice there is a claim structure referred to as a "dangling valence claim". This is a partial chemical structure (radical) with open bonding areas to which undisclosed moieties may attach forming many different types of compounds. The PTO Board of Appeals in *Ex Parte Diamond, 123 USPQ 167 (POBA 1959)* criticized claims relying upon dangling valence radicals as not providing support for the breadth of structures within the scope of the claims. It appears that considerations regarding the expansion of the dangling valence radical to form larger molecules of varying size and properties is analogous to the expansion of the SEQ ID NO: molecule when placed in a comprising claim format. The PTO is requested to evaluate nucleic acid or protein claims in "comprising" format from the context of how dangling valence claims are handled in chemical practice.

B) Considerations Regarding "Consisting Essentially Of" Language

The guidelines define "consisting essentially of" as a claim transition format that occupies a middle ground between closed "consisting of" and fully open "comprising" language. The accepted standard for this intermediate format is defined also in the guidelines to permit unlisted ingredients that do not materially affect the basic and novel properties of the invention. There are two issues relative to using "consisting essentially of" language that the NIH sets forth for consideration.

One issue is how this intermediate transitional language should be interpreted in nucleic acid and protein claims. As seen previously, open claim language changes the structure of a DNA or protein sequence by extension of the ends of molecules. Consistent with its definition, therefore, "consisting essentially of" also extends the termini of these molecules, but no more than would affect the basic and novel properties of the invention. As we know from *In re Papesch*, chemical properties are inseparable from the actual structure of the compound. Therefore, understanding how modifications at the termini of DNA or protein molecules effect functional properties is critical to proper application of this transitional claim language. Again, we learn from *In re Papesch* that this determination of material effect cannot be extrapolated from a mere formula or sequence, but must be empirically established for each compound.

Example 6 of the Training Materials provides an excellent illustration of a specification that teaches a probe utility of a DNA sequence that can accommodate an additional five to ten additional nucleotides on either end of the disclosed sequence structure. The note at the end of the example describes how to properly claim this embodiment using "consisting essentially of" language. The example teaches that this intermediate claim construction must be coupled with an express determination in the prosecution record that "consisting essentially of" admits of no more than 10 additional residues at either end of the molecule. This statement establishes for the record specific properties of the DNA molecule structure that permits definition of the boundaries for a material effect. Consequently, the use of "consisting essentially of" language in

DNA or protein claims should be coupled with a reference to specific structural properties or parameters that establish a material effect.

The second issue regarding intermediate transitional language relates to a statement in endnote 27 of the guidelines that threatens the well conceived teachings regarding "consisting essentially of" in Example 6. This statement reads, "[f]or search and examination purposes, absent a clear indication in the specification of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to 'comprising.'" This proposition is identified as supported by *PPG, 48 USPQ2d 1351, 1355 (Fed .Cir. 1998)* which teaches that, "PPG could have defined the scope of the phrase 'consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention." It is respectfully submitted that the above passage does not accurately reflect the context of usage in the case so as to lead to the conclusion that "consisting essentially of" should be construed as equivalent to "comprising". Following the cited passage from *PPG*, the court raised the following query: "The question for our decision is whether PPG did so." The determination on the facts was that *PPG* did not make clear in the specification what it regarded as constituting a material change. As a result, they were not granted the scope they sought based upon the use of "consisting essentially of" transition language, and their infringement claim was denied. Indeed, on page 356, the court denied *PPG's* proposed definition of a significant change noting that, "If that definition of 'significant effect' where adopted, it would have the effect of converting the critical claim language from 'consisting essentially of' to 'comprising'." Therefore, this conversion of "consisting essentially of" to "comprising" in the absence of an adequate disclosure to support the proper use of "consisting essentially of" is diametrically opposite to the intent of the decision.

In light of the criticisms associated with the use of "comprising" language in DNA and protein claims discussed above, it is illogical to move toward that condition. The specification and claims should be subject to criticism under Section 112, first paragraph if the specification is deficient in disclosing basic and novel characteristics of the invention. It is not advantageous to provide the Examining Corps mixed messages as to the appropriate meaning of this intermediate transitional term. The PTO is requested to revisit the *PPG* decision, and modify the faulty conclusion drawn in endnote 27.

In conclusion, the NIH thanks the PTO for the opportunity to present our views. Furthermore, the NIH appreciates the ongoing interactions between our sister agencies related to these written description and utility issues. The NIH believes these interactions have been beneficial in fostering understanding and appreciation of our respective missions, goals, and interests. We hope the comments contained in this communication further advance and refine the extraordinary

accomplishment of the PTO in developing guidelines for these difficult issues critical to development of biotechnology. Please feel free to contact us, if we can be of further assistance.

Sincerely,

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