UNITED STATES PATENT AND TRADEMARK OFFICE

# Patent Examination Policy - MPEP Staff - 35 USC 112 1st para - Enablement of Chemical/Biotechnical Applications

TRAINING MATERIALS FOR EXAMINING PATENT APPLICATIONS WITH RESPECT TO 35 U.S.C. SECTION 112, FIRST PARAGRAPH-ENABLEMENT OF CHEMICAL/BIOTECHNICAL APPLICATIONS

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# TRAINING MATERIALS FOR EXAMINING PATENT APPLICATIONS WITH RESPECT TO 35 U.S.C. SECTION 112, FIRST PARAGRAPH-ENABLEMENT CHEMICAL/BIOTECHNICAL APPLICATIONS

# I. LEGAL JUSTIFICATION

# A. CONSTITUTIONAL AUTHORITY

Requiring an applicant to provide information about the invention in his patent application to **enable** any person skilled in the art to make and use the invention is just one aspect of the "quid pro quo" for obtaining the legal right to exclude others from making, using, selling, offering for sale, or importing the claimed invention. The right to exclude others is the personal property right of the patent owner and is not granted by the government without the public obtaining a public good, i.e., the promotion of the progress of science and the useful arts. The founding fathers of the United States of America recognized the public good that would flow from the promotion of science and the useful arts and specifically granted Congress the authority to establish a patent system.

Authority for Congress to establish the United States patent system is based in the United States Constitution which provides in pertinent part:

The Congress shall have Power . . . to promote the Progress of Science and Useful arts, by securing for a limited Time to Authors and Inventors the exclusive Right to their respective Writings and Discoveries . . . . Article I, Section 8.

With this constitutional authority, Congress enacted Title 35 of the United States Code establishing the patent laws for the United States of America. Simply granting patents does not necessarily promote science and the useful arts. Rather, promotion of the progress of science and the useful arts is achieved by granting a patent in exchange for the public disclosure of the invention. Thus, Congress required more than a mere disclosure of the invention; Congress also required the inventor to teach the public how to make and use the invention as well. This requirement ensures that the invention will be available to the public once the patent term expires.

# B. STATUTORY MANDATES

The requirement that the inventor adequately disclose his invention to obtain the right to exclude others from making, using, selling, offering for sale, or importing the claimed invention is mandated by 35 U.S.C. Section 112.

Section 112, first paragraph, provides:
The **specification** shall contain a **written description of the invention** , and of the **manner and process of making and using it** , in such full, clear, concise, and exact terms as **to enable any person skilled in the art to which it pertains** , or with which it is most nearly connected, **to make and use the same** , and shall **set forth the best mode** contemplated by the inventor of carrying out his invention. (Emphasis added.)

The emphasized terms are the three requirements from Section 112, first paragraph, that the patent specification must meet in order to be a valid patent. An "enabling" disclosure is only one of the three requirements for the specification.

In addition to being an "enabling" disclosure, the specification must also provide an adequate "written description" of the invention and must disclose the embodiment of the invention that the inventor believes to be the "best mode" of the invention. The written description and best mode requirements are separate and distinct from the enablement requirement. *Vas-Cath Inc. v. Mahurkar* , 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116-17 (Fed. Cir. 1991); and MPEP Section 2161.

A working definition for the written description and best mode requirements are provided below only to assist in distinguishing these additional specification requirements from the enablement requirement.

The "written description" requirement requires the inventor to clearly convey to those skilled in the art through the specification the information that the applicant has invented as the specific subject matter of the claims. *In re Wertheim* , 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Although the applicant does not have to describe the subject matter claimed in the specification using exactly the same words used in the claims, the description must be sufficiently clear to allow one of ordinary skill to recognize that the applicant invented what is claimed. *In re Lukach* , 442 F.2d 967, 969, 169 USPQ 795, 796 (CCPA 1971); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

The "best mode" requirement mandates that the applicant disclose in the specification the "best mode" or the best way known to the inventor at the time of filing the application for carrying out the invention. Even though disclosing the best mode is a statutory requirement, it is unlikely that an examiner would ever have sufficient evidence to raise any doubt about whether the best mode has been disclosed.

# II. OVERVIEW OF EXAMINATION

## A. PROCEDURAL

Examination begins with a thorough review of the application in its entirety and with a preliminary determination of the scope of the claims. The examiner needs to determine what the claims recite and determine the meaning of each claim as a whole . The analysis should be systematic so that no claim is overlooked. The scope of dependent claims should be determined in addition to the scope of the independent claims. "A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers." 35 U.S.C. Section 112, fourth paragraph.

After the application has been read and the claimed invention understood, a prior art search for the claimed invention is made. With the results of the prior art search, including any references provided by the applicant, the patent application should be reviewed and analyzed in conjunction with the state of the prior art to determine whether the claims define a novel, non-obvious, and enabled invention that has been clearly described in the specification. The goal of examination is to clearly articulate any rejection early in the prosecution process so that the applicant has the opportunity to provide evidence of patentability and otherwise respond completely at the earliest opportunity. The examiner then reviews all the evidence, including arguments and evidence responsive to any rejection before issuing a Notice of Allowance or a final rejection.

These training materials provide the analytical framework and a discussion of relevant factors that the examiner should consider when determining whether there is sufficient evidence to support a determination that the specification does not enable one skilled in the art to make and use the claimed invention.

# B. ASSUMPTIONS/ BURDEN ON THE EXAMINER

When rejecting a claim under the enablement requirement of section 112, the examiner bears the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright* , 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the examiner must provide evidence or technical reasoning substantiating those doubts. Id. ; and MPEP Section 2164.04.

Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright* , 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Marzocchi* , 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). The burden placed on the examiner is reflected in the MPEP Section 706.03.

Accordingly, the case law makes clear that properly reasoned and supported statements explaining any failure to comply with Section 112 are a requirement to support a rejection. *In re Wright* , 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

# III. DETERMINING WHETHER THE ENABLEMENT REQUIREMENT IS MET

In making the determination of enablement, the examiner shall consider the original disclosure and all evidence in the record, weighing evidence that supports enablement against the evidence that the specification is not enabling.

In the mid-1800's the Supreme Court reasoned that a specification would be defective if it required one with skill to "experiment" in order practice the claimed invention. *Wood v. Under Hill,* 46 U.S. (4 How.) 1 (1847 *).* The standard for determining whether the specification met the enablement requirement was recast in the later Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands* , 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in art can make and use the invention without undue experimentation. *In re Wands* , 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

1. the breadth of the claims,
2. the nature of the invention,
3. the state of the prior art,
4. the level of one of ordinary skill,
5. the level of predictability in the art,
6. the amount of direction provided by the inventor,
7. the existence of working examples, and
8. the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement).

In *Wands* , the court noted that the there was no disagreement as to the facts, but merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts. *In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1403-07. The court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." Id. at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." Id. , 8 USPQ2d at 1407.

It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole. Id. at 737 & 740, 8 USPQ2d at 1404 & 1407.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright* , 999 F.2d at 1562, 27 USPQ2d at 1513.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. These factual considerations are discussed more fully below.

# A. NECESSARY FACTORS TO EVALUATE

**Before any analysis of enablement can occur, it is necessary for the examiner to construe the claims. For terms that are not well-known in the art, or for terms that could have more than one**

**meaning, it is absolutely necessary that the examiner select the definition that he/she intends to use when examining the application, based on his/her understanding of what applicant intends it to mean, and explicitly set forth the meaning of the term and the scope of the claim when writing an Office action. See G *enentech v. Wellcome Foundation,* 29 F.3d 1555, 1563-64, 31 USPQ2d 1161, 1167-68 (Fed. Cir. 1994).**

## 1. Scope/ Breadth of the Claims

Determining whether the enablement requirement has been met requires analyzing the claim to determine its scope.

All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. The examiner should determine what each claim recites and what the subject matter is when the claim is considered as a whole , not when its parts are analyzed individually. No claim should be overlooked. With respect to dependent claims, Section 112, fourth paragraph, of Title 35 should be followed. This paragraph states that "a claim in a dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers" and requires the dependent claim to further limit the subject matter claimed.

The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner* , 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. E.g. , *In re Fisher* , 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

In this regard, MPEP Section 2164.08 provides, in pertinent part, as follows.

As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore* , 439 F.2d 1232, 169 USPQ 236 (CCPA 1971)
The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of the enablement involves two stages of inquiry. The first is to determine how broad the claim is with respect to the disclosure. The entire claim must be considered. The second inquiry is to determine if one skilled in the art is [sic, would have been] enabled to make and use the entire scope of the claimed invention without undue experimentation.

. . .

If a rejection is made based on the view that the enablement is not commensurate in scope with the claim, **the examiner should identify the subject matter that is considered to be enabled.** [Emphasis added.]

One does not look to the claims but to the specification to find out how to practice the claimed invention. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.,* 721 F.2d 1540, 1558, 220 USPQ 303, 316-17 ( Fed. Cir. 1983); *In re Johnson* , 558 F.2d 1008, 1017, 194 USPQ 187, 195 (CCPA 1977). In *In re Goffe* , 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated:

to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

When analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification. "That claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims." *Raytheon Co. v. Roper Corp.,* 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 835 (1984).

Part of the examiner's job is to clarify the record so that the public will have notice as to the patentee's scope of protection when the patent issues. If a reasonable interpretation of the claim is broader than the description in the specification, it is necessary for the examiner to take the additional time and effort to make sure the full scope of the claim is enabled. Limitations and examples in the specification do not generally limit what is covered by the claims. Consequently, if the claim is to a method of transforming cells and the broadest reasonable interpretation of the claim includes transforming cells *in vivo* for gene therapy, the examiner must make a determination as to whether there is sufficient evidence to support a conclusion that such scope is not enabled. If applicants intended only *in vitro* use, such a limitation should appear in the claims.

The breadth of the claims was a factor considered in *Amgen v. Chugai Pharm. Co.* , 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), *cert. denied* , 502 U.S. 856 (1991). In the *Amgen* case, the patent claims were directed to a purified DNA sequence encoding polypeptides which are analogs of erythropoietin (EPO). The court stated that:

Amgen has not enabled preparation of DNA sequences sufficient to support its all-encompassing claims. . . . [D]espite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analog genes are disclosed. . . . This disclosure might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO gene analogs. There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them. 927 F.2d at 1213-14, 18 USPQ2d at 1027.

The court in *Amgen* focused on the fact that the claims were directed to DNA sequences that encoded amino acid sequences, wherein the amino acid sequences had substitutions but preserved a particular physiological activity. Thus, the amino acid sequences mentioned in the claims in *Amgen* were of differing scope. Additionally, the specification did not give those skilled in the art guidance as to which amino acids could be changed to either preserve or enhance the activity of the protein. Because a very small change in

the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the distant future.

Similarly, in *In re Wright* , 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993), the court affirmed the Board's decision and stated that the evidence did not show that a skilled artisan would have been able to carry out the steps required to practice the full scope of claims which encompass " any and all live, non-pathogenic vaccines, and processes for making such vaccines, which elicit immunoprotective activity in any animal toward any RNA virus." 999 F.2d at 1562, 27 USPQ2d at 1513 (original emphasis).

In *In re Goodman* , 11 F.3d 1046, 1052, 29 USPQ2d 2010, 2015 (Fed. Cir. 1993), the claims were directed to a method for producing mammalian peptides in plant cells by the integration of a DNA construct encoding mammalian peptide into plant cells. The court, in affirming the Board's decision, found that the specification did not support the broad scope of the claims because the specification contained only an example of producing gamma-interferon in a dicot species; and there was evidence that extensive experimentation would have been required for encoding mammalian peptide into a monocot plant at the time of filing. Thus, the application would not have enabled one of skill in the field of biotechnology to produce any type of mammalian peptide in any plant cell as broadly claimed.

## 2. Reasons For Lack Of Enablement: Undue Experimentation Needed To Make And Use The Invention

### a. Points of Reference

Whether the specification would have been enabling as of the filing date involves many of the same considerations that are evaluated for determining whether or not the claimed invention would have been obvious as of the date it was invented. These considerations are: the nature of the invention, the state of the prior art, and the level of skill in the art. These considerations are reviewed here briefly in summary form to assist the explanation of the enablement analysis.

### i. Nature of the Invention

The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art.

### ii. State of the Art

The state of the prior art is what one skilled in the art a would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled; however, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date.

## (a) Relevant Art

Section 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." In general, the pertinent art should be defined in terms of the problem to be solved rather than in terms of the technology area, industry, trade, etc. for which the invention is used.

## (b) Well-Known Information

The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner* , 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies , Inc .* , 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied* , 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.* , 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

## iii. Level of Skill

The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed.

## b. Amount of Direction or Guidance Present: Sufficiency of Disclosure / Predictability/ Non-Predictability

The "amount of guidance or direction present" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* , 427 F.2 833, 839, 166 USPQ 18, 24 (CCPA 1970). The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.

The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi* , 439 F.2d 220, 223-24, 169 USPQ 367, 368-70 (CCPA 1971), stated:

[i]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]

The predictability in the art is inversely related to the amount of guidance or direction needed for enablement. In other words, art areas that are predictable require less guidance or direction for enablement than art areas that are not predictable. *In re Fisher* , 427 F.2 833, 839, 166 USPQ 18, 24 (CCPA 1970).

## i. How to Make

## (a) One Method is Sufficient

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of Section 112 is satisfied. *In re Fisher* , 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under Section 112. *Spectra-Physics, Inc. v. Coherent, Inc* . 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), *cert. denied* , 484 U.S. 954 (1987).

Naturally, for unstable and transitory chemical intermediates, the "how to make" requirement does not require that the applicant teach how to make the claimed product in stable, permanent or isolatable form. *In re Breslow* , 616 F.2d 516, 521, 205 USPQ 221, 226 (CCPA 1980).

## (b) Availability of Starting Materials and Apparatus

A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. This is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening.

The CCPA in *In re Ghiron* , 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. *In re Howarth,* 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

The problem with the availability of starting materials when the product or process requires the use of a particular strain of microorganisms is addressed in separate training materials relating to depositing a sample of a microorganism with an independent depository.

## (c) Isolated DNA for Purified Protein ( ***In re Deuel*** )

When claims are directed to any purified and isolated DNA sequence encoding a specifically named protein wherein the protein has a specifically identified sequence, a scope rejection is generally not appropriate.

In *In re Deuel* , 51 F.3d 1552, 1560, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995), the court stated:

Because Deuel's patent application does not describe how to obtain any DNA except the disclosed cDNA molecules, claims 4 and 6 may be considered to be inadequately supported by the disclosure of the application. *See generally Amgen Inc. v. Chugai Pharmaceutical Co.* , 927 F.2d 1200, 1212-24, 18 USPQ2d 1016, 1026-28 (Fed. Cir.) (generic DNA sequence claims held invalid under 35 U.S.C. § 112, first paragraph), *cert. denied* , 502 U.S. 856 (1991); *In re Fisher* , 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (Section 112 "requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art"). As this issue is not before us, however, we will not address whether claims 4 and 6 satisfy the enablement requirement of § 112, first paragraph, but will leave to the PTO the question whether any further rejection is appropriate.

The court in *Deuel* left it to the PTO to decide whether a scope rejection would be appropriate. Responsive to the issue left open by the Federal Circuit in *Deuel* , the PTO has decided that scope rejections like those noted above should not be advanced for claims like those in *Deuel* .

The *Deuel* claims 4 and 6 were directed to any DNA that would encode a specific amino acid sequence. Claims 4 and 6 recited only one amino acid sequence each and each claim was directed to all nucleic acid sequences that encode the respective amino acid sequence. The various genetic codes are well-known. Thus, to list all cDNA of the sequences that encode a given amino acid sequence simply requires reverse translating the amino acid sequence to the nucleic acid sequence. Theoretically, one armed only with a pencil, paper, and the genetic code could list all of the cDNA that encode the two amino acid sequences mentioned in the claims. Admittedly, this could not be done in practice even by a fast computer because claim 4 embraces 2.09 x 1075 embodiments. However, any one of the embodiments could be readily determined. As to actually obtaining the cDNA, this could be done by simply writing down the sequence and ordering it from a company that custom synthesizes DNA.

## ii. How to Use

If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. Section 112, is satisfied. *In re Johnson* , 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); and *In re Hitchings* , 342 F.2d 80, 87, 144 USPQ 637, 643

(CCPA 1965); see also *In re Brana,* 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).

It is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an

appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. Section 112. The applicant need not demonstrate that the invention is completely safe. See also 35 U.S.C. Section 103 , Utility Guidelines.

## (a) Use Recited in the Claims

When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck* , 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)(claiming a chimeric gene capable of being expressed in any cyanobacterium and thus defining the claimed gene by its use).

In contrast, when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

The following examples illustrate the application of these standards.

1. The claim: A composition for treating Alzheimer's disease comprising a compound having the formula X" (where X is specifically defined within the claim). Assuming it is clear from the specification and/or applicant's arguments that the claimed composition is limited to treating Alzheimer's disease, the enablement issue is whether one skilled in the art could have made or used the composition for treating Alzheimer's disease without undue experimentation, at the time the application was filed. The enablement analysis should be based on whether there is evidence that one skilled in the art could not have used the compound for treating Alzheimer's disease without undue experimentation. If the statement of use is only a statement of one intended use, then the claim should be treated as in example 2.
2. The claim: A composition comprising a compound having the formula X (where X is specifically defined within the claim). The enablement issue is whether one skill in the art could have made or used the composition for any disclosed or well-established use without undue experimentation, at the time the application was filed. The enablement analysis should be based on whether there is evidence that one skilled in the art could not have used the compound for any disclosed or well-established use undue experimentation.
3. The claim: A composition comprising a compound having the formula X in a pharmaceutically acceptable carrier (where X is specifically defined within the claim). The specification discloses both an *in vitro* and *in vivo* use for the composition.

The presence of the phrase "pharmaceutically acceptable" in combination with the disclosed *in vivo* use implies some pharmaceutical use . Therefore, the initial enablement analysis should be based on whether there is any evidence that one skilled in art could not use the compound for any disclosed or well-

established pharmaceutical use, i.e., treatment of some disease or condition *in vivo* , without undue experimentation. Any subsequent enablement analysis should be based on the claim language, what is taught in the specification, as well as any rebuttal arguments.

All rebuttal arguments must be considered. The weight the evidence and each argument should be given will depend on the facts of the case. Assuming that the applicants rebuttal is persuasive, the 35 U.S.C. Section 112, first paragraph, rejection should be withdrawn. The persuasiveness of any evidence and arguments clearly depends on the specific language of the claim, the teachings in the specification and the evidence submitted in rebuttal to the rejection.

## (b) Diagnosis Assays

Unless a specification specifically states something to the contrary, the term "diagnostic assay" is to be construed to mean any assay that can be used to help diagnose a condition, as opposed to an assay that can, in and of itself, diagnose a condition. A diagnosis is typically made by evaluating the results of several screening assays, each of which has some level of false results and, accordingly, each of the screening assays would be a "diagnostic assay". Therefore, to enable a diagnostic assay use, a disclosure merely needs to teach how to make and use the assay for screening purposes.

## © Several Decisions Ruling that the Disclosure was Non-Enabling

The following summaries should not be relied upon to support a case of lack of enablement without carefully reading the case.

1. In *In re Wright* , 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993), the 1983 application disclosed a vaccine against the RNA tumor virus known as Prague Avian Sarcoma Virus, a member of the Rous Associated Virus family. Using functional language, Wright claimed a vaccine "comprising an immunologically effective amount" of a viral expression product. Id. at 1559, 27 USPQ2d at 1511. Rejected claims covered all RNA viruses as well as to avian RNA viruses. The Examiner provided a teaching that in 1988, a vaccine for another retrovirus (i.e., AIDS) remained an intractable problem. This evidence, along with evidence that the RNA viruses were a diverse and complicated genus, convinced the Federal Circuit that the invention was not enabled for either all retroviruses or even for avian retroviruses.
2. In *In re Goodman* , 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993), a 1985 application functionally claimed a method of producing protein in plant cells by expressing a foreign gene. The court stated: "[n]aturally, the specification must teach those of skill in the art 'how to make and use the invention as broadly as it is claimed.'" Id. at 1050, 29 USPQ2d at 2013. Although protein expression in dicotyledonous plant cells was enabled, the claims covered any plant cell. The examiner provided evidence that even as late as 1987, use of the claimed method in monocot plant cells was not enabled. Id. at 1051, 29 USPQ2d at 2014.
3. In *In re Vaeck* , 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), the court found that several claims were not supported by an enabling disclosure "[t]aking into account the relatively incomplete understanding of the biology of cyanobacteria as of appellant's filing date, as well as the limited disclosure by appellants of the particular cyanbacterial genera operative in the claimed invention. . . ."

The claims at issue were not limited to any particular genus or species of cyanbacteria and the specification mentioned nine genera and the working examples employed one species of cyanobacteria.

4. In *In re Colianni* , 561 F.2d 220, 222-23,195 USPQ 150, 152 (CCPA 1977), where the court affirmed a rejection under Section 112, first paragraph, because the specification directed to a method of mending a fractured bone by applying "sufficient" ultrasonic energy to the bone did not define a "sufficient" dosage or teach one of ordinary skill how to select the appropriate intensity, frequency, or duration of the ultrasonic energy.

## (d) Several Decisions Ruling that the Disclosure was Enabling

The following summaries should not be relied upon to support a case of lack of enablement without carefully reading the case.

1. In *PPG Ind. v. Guardian Ind., 75* F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), the court ruled that even though there was a software error in calculating the ultraviolet transmittance data for examples in the specification making it appear that the production of a cerium oxide-free glass that satisfied the transmittance limitation would be difficult, the specification indicated that such glass could be made. The specification was found to indicate how to minimize the cerium content while maintaining low ultraviolet transmittance.
2. In *In re Wands* , 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the court reversed the rejection for lack of enablement under Section 112, first paragraph, concluding that undue experimentation would not be required to practice the invention. The nature of monoclonal antibody technology is such that experiments first involve the entire attempt to make a monoclonal hybridomas to determine which ones secrete antibody with the desired characteristics. The court found that the specification provided considerable direction and guidance on how to practice the claimed invention and presented working examples, that all of the methods needed to practice the invention were well known, and that there was a high level of skill in the art at the time the application was filed. Furthermore, the applicant carried out the entire procedure for making a monoclonal antibody against HBsAg three times and each time was successful in producing at least one antibody which fell within the scope of the claims.
3. In *In re Bundy* , 642 F.2d 430, 434, 209 USPQ 48, 51-52 (CCPA 1981), the court ruled that the claimed analogs of naturally occurring prostaglandins had certain pharmacological properties even though the specification lacked any examples of specific dosages, but did state that the novel compound possessed activity similar to E-type prostaglandins.

## c. Presence or Absence of Working Examples (Make or Use)

The presence of a working examples demonstrates the making or using of the invention. However, working examples are not required by the statute, rules, or the case law.

## i. None or One Working Example

The lack of working examples is one consideration in the overall analysis of lack of enablement. *In re Colianni* , 561 F.2d at 224, 195 USPQ at 153. The MPEP, Section 2164.02, states: "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation."

When considering the factors relating to a determination of non-enablement, if all the other factors point toward enablement, then the absence of working examples will not by itself render the invention non-enabled. In other words, lack of working examples or lack or evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement. A single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled. However, a rejection stating that enablement is limited to a particular scope may be appropriate.

The presence of only one working example should never be the sole reason for making a scope rejection, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims.

## ii. Correlation: ***In Vitro/In Vivo***

The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" for purposes of this portion of the training materials refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana* , 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)(reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

Since the initial burden is on the examiner to give reasons for the lack of enablement, when possible to supported by evidence, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka* , 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

## iii. Working Examples and a Claimed Genus

For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art-in view of level of skill, state of the art and the information in the specification-would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

## d. Quantity of Experimentation

The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A] n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni* , 561 F.2d at 224,195 USPQ at 153. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' *In re Wands* , 858 F.2d at 737, 8 USPQ2d at 1404 (citing *In re Angstadt* , 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectonics Inc.,* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied* , 490 U.S. 1046 (1989).

In the chemical arts, the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of a claim, then this great quantity of experimentation should be considered in the overall analysis. Time and difficulty of experiments are not determinative if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands* , 858 F.2d at 737, 8 USPQ2d at 1404.

## i. Example of Reasonable Experimentation

In *United States v. Telectonics Inc.,* 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied* , 490 U.S. 1046 (1989), the court reversed the findings of the district court for lack of clear and convincing proof that undue experimentation was needed. The court ruled that since one embodiment (stainless steel electrodes) and the method to determine dose/response was set forth in the specification, the specification was enabling. The question of time and expense of such studies, approximately $50,000 and 6-12 months standing alone, failed to show undue experimentation.

## ii. Example of Unreasonable Experimentation

In *In re Ghiron* , 442 F.2d at 991-92, 169 USPQ at 727-28, functional "block diagrams" were insufficient to enable a person skilled in the art to practice the claimed invention with only a reasonable degree of experimentation because the claimed invention required a "modification to prior art overlap computers," and because "many of the components which appellants illustrate as rectangles in their drawing necessarily are themselves complex assemblages . . . . It is common knowledge that many months or years

elapse from the announcement of a new computer by a manufacturer before the first prototype is available. This does not bespeak of a routine operation but of extensive experimentation and development work . . . ."

### e. Supplementing a Disclosure

The specification may be enabling even though amendments may be needed. Such amendments often occur when the applicant incorporates information by reference into the specification or uses a trade name or trademark to provide descriptive information.

### i. Incorporating by Reference

The Commissioner has considerable discretion to permit the applicant to incorporate information by reference into the specification. The information incorporated by reference at the time of filing is as much a part of the application as filed as if the text were repeated therein. Editing the application by inserting verbatim that which was previously only incorporated by reference does not raise new matter issues. *In re Hawkins,* 486 F.2d 569, 574, 179 USPQ 157, 161 (CCPA 1973); and MPEP Sections 608.01(p) and 2163.07 (b).

### ii. Use of Trademarks: Potential4Future Non-enablement

When the applicant refers to materials, products or processes, etc. by their respective trade name or trademark in the specification, the examiner should require that a generic description be inserted in place of, or in addition to, a trade name or trademark. This is necessary since the owner of the product to which the trade name or trademark refers can change the product over time. Such future decisions are often outside the control of the applicant. If such a change occurred, the trade name or trademark could come to represent different things at different points in time with no way learning what the differences were. Whether the use of a trade name or trademark provides sufficient description and disclosure of the claimed invention must be decided on a case-by-case basis. Where the identification material or apparatus referred to by its trademark or trade name is introduced by amendment, the information must be restricted to the characteristics of the product known at the time the application was filed to avoid any question of new matter. *In re Metcalfe* , 410 F.2d 1378, 1382, 161 USPQ 789, 792 (CCPA 1969); and MPEP Section 608.01(v).

## B. UTILITY AND OPERABILITY

### 1. Preferred Materials in Specification Need not be in the Claims

Limiting an applicant to the preferred materials in the absence of limiting prior art would not serve the constitutional purpose of promoting the progress in the useful arts. Therefore, an enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim should be made only when the language of the specification makes it clear that the limitation is critical for the invention to function as intended. Broad language in the disclosure, including the abstract, omitting an allegedly critical feature, tends to rebut the argument of criticality.

### 2. Inoperability/Inoperative Species within the Scope of the Claim

The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. duPont de Nemous & Co.* , 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)(prophetic examples do not make the disclosure non-enabling). Although, typically, inoperative embodiments are excluded by language in a claim the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. *In re Angstadt,* 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976); and MPEP Section 2164.08(b). However, claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Atlas Powder Co. v. E.I. duPont de Nemous & Co.* , 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); *In re Cook,* 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971); see also MPEP Section 2164.08(b).

# C. LACK OF ENABLEMENT IN VIEW OF AN OBVIOUSNESS REJECTION

Many times an Office action will contain both a 35 U.S.C. Section 112, first paragraph, enablement rejection and a prior art rejection under 35 U.S.C. Section 102 and/or 103 against the same claim. In such cases, the examiner has determined that the claimed invention is not enabled and yet is anticipated or prima facie obvious in view of prior art. The presence of both rejections in an Office action against the same claim appears contradictory. However, it is not necessarily a contradiction or an improper Office action. The following examples illustrate scenarios where both can coexist.

1. A claim recites a genus but the specification is enabling only for species X. A reference found by the examiner provides evidence that the specification is enabling for species X only and discloses species X. In this case, a scope rejection stating that the claims should be limited to species X is appropriate as is a 102 rejection.
2. A claim recites a genus. The specification discloses only one use for the genus and demonstrates only species X for that use. The examiner finds a first reference that supports the position that it would require undue experimentation to use members of that genus other than species X for the only disclosed purpose. The examiner also finds a second reference that suggests another member, species Y, of the genus for a different purpose. In this case, a scope rejection stating that the claim should be limited to species X is appropriate as is a Section 103 rejection stating that species Y would have been obvious. These rejections are not contradictory.
3. A claim recites a method of treating HIV infection in a human by administering X to the human. The specification discloses an *in vitro* assay which demonstrates that X will inhibit HIV replication. The examiner finds five references to support the position that treating HIV is unpredictable and that *in vitro* models do not reasonably correlate to *in vivo* treatment. The examiner also finds a sixth reference

that demonstrates that X will inhibit HIV replication *in vitro* and suggests treating HIV infection in a human byadministering X to the human. In this case, a lack of enablement rejection would be appropriate using the five references as support. A Section 103 rejection using the sixth reference would also be appropriate. Admittedly, the rejections are contradictory. Nevertheless, in view of the contradictory nature of the suggestions in the state of the art, the contradictory rejections are appropriate since one position is likely to be correct. This type of treatment should be limited to those art areas in which the teachings and suggestions in the art are in conflict with one another.

# D. THE INVENTION MAY BE ENABLED BUT NOT ADEQUATELY DESCRIBED

The enablement requirement of 35 U.S.C. Section 112, first paragraph, is separate and distinct from the description requirement. *Vas Cath Inc. v. Mahurkar* , 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116-17 (Fed. Cir. 1991)("the purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'"); and MPEP Section 2161. Therefore, the fact that an additional limitation to a claim may lack descriptive support in the disclosure as originally filed does not necessarily mean that the limitation is also not enabled. In other words, the statement of a new limitation in and of itself may enable one skilled in the art to make and use the claim containing that limitation even though that limitation may not be described in the original disclosure. Consequently, such limitations must be analyzed for both enablement and description using their separate and distinct criteria.

Furthermore, when the subject matter is not in the specification portion of the application as filed but is in the claims, the limitation in and of itself may enable one skilled in the art to make and use the claim containing the limitation. When claimed subject matter is only presented in the claims and not in the specification portion of the application, the specification should be objected to for lacking the requisite support for the claimed subject matter using Form Paragraph 7.44. See MPEP Section 2163.06. This is a technical rejection only and enablement issues should be treated separately.

Form Paragraph 7.44 provides:

CLAIMED SUBJECT MATTER NOT IN SPECIFICATION

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFI 1.75(d)(1) and MPEP 608.01(1). Correction of the following is required: [1].

# IV. COMMUNICATING FINDINGS TO THE APPLICANT

# A.THE LEVEL OF DETAIL

While the analysis and conclusion are based on all the above factors and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation , or that the scope of any

enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can easily be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. MPEP § 2164.06. References should be supplied if possible to support a *prima facie* case of lack of enablement, but are not always required. *In re Marzocchi* , 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

In accordance with the principles of compact prosecution, if an enablement rejection is appropriate, the first Office action on the merits should present the best case with all the relevant reasons, issues, and evidence so that all such rejections can be withdrawn if applicant provides appropriate convincing arguments and/or evidence in rebuttal. Providing the best case in the first Office action will also allow the second Office action to be made final should applicant fail to provide appropriate convincing arguments and/or evidence. Citing new references and/or expanding arguments in a second Office action could prevent that Office action from being made final. The principles of compact prosecution also dictate that if an enablement rejection is appropriate and the examiner recognizes limitations that would render the claims enabled, the examiner should note such limitations to applicant as early in the prosecution as possible.

In other words, the examiner should always look for enabled, allowable subject matter and communicate to applicant what that subject matter is at the earliest point possible in the prosecution of the application.

# B. THE FORM PARAGRAPHS

The relevant form paragraphs that should be used when making a rejection for lack of enablement are paragraphs 7.31.02, 7.31.03, or 7.33.01. See MPEP § 706.03©. Regardless of which Form paragraph is used, the examiner must always clearly articulate the reasons for his or her belief that an enablement issue exists and cite to the evidence that supports his or her belief .

## 1 35 U.S.C. 112,1st, Enablement 7.31.02

Form paragraph 7.31.02 is to be used when it is the examiner's position that nothing within the scope of the claims is enabled. In such a rejection, the examiner should explain all the reasons why nothing within the scope of the claims is enabled. To make sure all relevant issues are raised, this should include any issues regarding the breadth of the claims relative to the guidance in the disclosure. Form paragraph 7.31.02 is as follows:

Claim **[1]** rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **[2]** the invention. **[3]** .

## Examiner Note:

1. If the problem is one of scope, form paragraph 7.31.03 should be used.
2. In bracket 2, fill in only the appropriate portion of the statute, i.e., one of the following "make," "use," or "make and use".
3. In bracket 3, identify the claimed subject matter for which the specification is not enabling along with an explanation as to why the specification is not enabling. The explanation should include any questions posed by the examiner which were not satisfactorily resolved and consequently raise doubt as to enablement.
4. Where an essential component or step of the invention is not recited in the claims, use form paragraph 7.33.01.

## 2. 35 U.S.C. 112, 1st, Scope Of Enablement 7.31.03

Form paragraph 7.31.03 is to be used when it is the examiner's position that something within the scope of the claims is enabled but the claims are not limited to that scope. Form paragraph 7.31.03 states:

Claim **[1]** rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **[2]** , does not reasonably provide enablement for **[3]** . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **[4]** the invention commensurate in scope with these claims. **[5]** .

### Examiner Note:

1. This paragraph is to be used when the scope of the claims is not commensurate with the scope of the enabling disclosure.
2. In bracket 2, identify the claimed subject matter for which the specification is enabling. This may be by reference to specific portions of the specification.
3. In bracket 3, identify aspect(s) of the claims(s) for which the specification is not enabling.
4. In bracket 4, fill in only the appropriate portion of the statute, i.e., one of the following: "make," "use," or "make and use".
5. In bracket 5, identify the problem along with an explanation as to why the specification is not enabling. The explanation should include any questions posed by the examiner which were not satisfactorily resolved and consequently raise doubt as to enablement.

## 3. 35 U.S.C. 112, 1st, Essential Subject Matter Missing From Claims (Enablement) , 7.33.01 :

Form paragraph 7.33.01 is to be used when it is the examiner's position that a feature that is critical or essential to the practice of the claimed invention is missing from the claim.

Form paragraph 7.33.01 states:

Claim **[1]** rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. **[2]** critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. *In re Mayhew* , 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). **[3]** .

### Examiner Note:

1. In bracket 2, recite the subject matter omitted from the claims.
2. In bracket 3, give the rationale for considering the omitted subject matter critical or essential.

3. The examiner shall cite the statement, argument, date, drawing, or other evidence which demonstrates that a particular feature was considered essential by the applicant, is not reflected in the claims which are rejected.

### 4. Multiple Use of Form Paragraphs

A claim should not be rejected using form paragraph 7.31.02 and also rejected using either form paragraph 7.31.03 or form paragraph 7.33.01 within the same Office action since this would present conflicting and confusing positions. Form paragraph 7.31.02 states that nothing is enabled in that claim and each of the other two form paragraphs state that something within the scope of the claim is enabled. If the examiner concludes that nothing is enabled for one reason and that the breadth of the claims is also not commensurate in scope with the guidance in the specification, then all these issues should be raised with respect to that claim using form paragraph 7.31.02. Sometimes the scope of a claim may not be enabled because a critical or essential feature is missing in addition to other reasons. In such cases, all the scope issues may be raised under form paragraph 7.31.03 or form paragraph 7.33.01, or the issues may be raised separately by using both form paragraph 7.31.03 and form paragraph 7.33.01.

### 5. Practical Tips in Writing the Rejection

- Look for enabled embodiments and, if found, communicate to applicant which embodiments are enabled.
- Be concise.
- Focus on those factors which lead to a conclusion of lack of enablement.
- Make express findings of fact related to the specific case.
- Emphasize specific technical reasons for the conclusion of lack of enablement.
- Tailor your discussion to the particulars of the claimed invention.
- Use no speculative phrases.
- Support statements with evidence and/or sound scientific reasoning.

## V. REBUTTAL TO THE REJECTION PROOF OF ENABLEMENT:

## EVIDENCE AND ATTORNEY ARGUMENT

Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art. A declaration or affidavit is, itself, evidence that must be considered.

To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed , would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date

which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope, i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation.

The examiner must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should **never** make the determination based on personal opinion. The determination should always be based on the weight of all the evidence.

## A. USE OF POST FILING DATE EVIDENCE

In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application. *In re Budnick,* 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976). Similarly, in general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to these rules could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. That is, if individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered.

## B. EXPERT DECLARATIONS

Declarations and affidavits are evidence . The weight to give them will depend upon the amount of factual evidence they contain to support the conclusion of enablement. *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"); *cf. In re Alton, 76* F.3d 1168, 1174, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996)(declarations relating to the written description requirement should have been considered).

## C. USE OF FDA SUBMISSIONS

An applicant may argue that the FDA has approved clinical trials and, therefore, the claims should be considered enabled by the specification. FDA approval is an important consideration. However, considerations made by the FDA for approving clinical trial are different from those made by the PTO in determining whether a claim is enabled. See *Scott v. Finney* , 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("[t]esting for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].")

Applicant should be encouraged to provide any evidence to demonstrate that the disclosure enables the claimed invention, including evidence actually submitted to the FDA to obtain approval for clinical trials. Once that evidence is submitted, it must be weighed with all other evidence according to the standards set forth above so as to reach a determination as to whether the disclosure enables the claimed invention.

# ENABLEMENT DECISION TREE


Enablement Decision Tree Diagram [link to full text]

**(/patent/laws-and-regulations/examination-policy/text-version-enablement-decision-tree)**

## Example A: Hybridization Probes I

**Specification:** The specification discloses that bacteria A is known to cause a specific disease and, therefore, detection of bacteria A in a sample is desirable. The specification even discloses that methods are known which detect bacteria A in a sample via culturing techniques. According to the specification, such detection methods are difficult to perform and therefore detection methods using nucleic acid probes are preferred.

The specification discloses that one object of the invention is to provide nucleic acids complementary to unique nucleic acid sequences within the RNA or DNA of bacteria A and which can be used to detect bacteria A. Another object of the invention is to provide a method of detecting bacteria A in a sample by contacting the sample with a probe which preferentially hybridizes to RNA or DNA of bacteria A but not to non-bacteria A organisms.

The term "probe" is described in the specification as a nucleic acid between 10 and 300 base pairs in length which contain specific nucleotide sequences that specifically and preferentially hybridize under predetermined conditions to nucleic acid sequences of bacteria A. The probes optionally contain a detectable moiety.

The following three specific probes were disclosed:

Bacteria A probe 1 (35mer) (SEQ ID NO:1)

5'-CATTAGAGTC GTACGTGCTA GACTGATTAA CCGGT-3'

Bacteria A probe 2 (33mer) (SEQ ID NO:2)

5'-CAATCCAGTA AGTTTTACCC GGCCAAATAA AGG-3'

Bacteria A probe 3 (30mer) (SEQ ID NO:3)

5'-AAATAGCCAG ATCATTGCCC CGGACCCTTG-3'

An example appears in the specification which demonstrates how to carry out the detection and which

shows that the three probes are specific for bacteria A and fail to hybridize to 50 other types of bacteria.

## Claims:

1. An isolated nucleic acid consisting of 10 to 300 nucleotides which hybridizes preferentially to RNA or DNA of bacteria A and not to non-bacteria A organisms, wherein said nucleic acid is or is complementary to a nucleotide sequence comprising at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3.
2. A probe comprising a nucleic acid of claim 1 and a detectable moiety.
3. A method of detecting the presence of bacteria A in a sample suspected of containing bacteria A comprising
4. 
    - a) contacting the sample with an isolated nucleic acid of claim 1,
    - b) imposing hybridization conditions on the sample and said isolated nucleic acid to allow the formation of a hybridization product between said nucleic acid and RNA or DNA from bacteria A, if present in the sample, but not from RNA or DNA from non-bacteria A bacteria; and
    - c) detecting any hybridization product as an indication of the presence of bacteria A in the sample.

**State of the Prior Art:** A search was carried out to compare the multitude of 10 nucleotide probes encompassed by the claims with sequences in the EMBL database with the following results:

**10,541 database hits for the 10mers of probe 1;**
**15,378 database hits for the 10mers of probe 2;**
**5,691 database hits for the 10mers of probe 3.**

Some of the hits for each probe were in the RNA or DNA of bacteria other than bacteria A, such as *Salmonella, Candida, and Streptococcus* .

Wallace et al, Methods Enzymol. 152:432-443 (1987).

Sambrook et al, Molecular Cloning, A Laboratory Manual , Second Edition, 1989, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, p. 11.47.

Wallace et al and Sambrook et al teach the empirical nature of determining the specificity of hybridization probes and the unpredictability of the effect of mismatches within an oligonucleotide probe.

The 50 different bacteria tested within the example in the specification are representative of bacteria in general.

## Analysis:

There is a demonstration in the specification that the three specifically disclosed probes can be used to detect bacteria A. Furthermore, the sequences of those probes are disclosed so that one skilled in the art could clearly make them. Therefore, the specification does teach how to make and use three

embodiments encompassed by the claims. Accordingly, an objection/rejection using form paragraph 7.31.02 would be inappropriate. The issue then is whether the enabled embodiments are representative of the scope of the claims.

Before this can be determined, the scope of at least claim 1 must be determined. Claim 1 recites three limitations on the nucleic acid, two structural and one functional. The two structural limitations are 1) that the nucleic acid consists of 10 to 300 nucleotides and 2) that the nucleic acid is or is complementary to a nucleotide sequence **comprising** at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3. Since the nucleotide sequence mentioned merely **comprises** at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3, it encompasses any random sequence of any length as long as it has a stretch of at least ten consecutive nucleotides that is the same as in SEQ ID NOS 1-3. Furthermore, since there is no limitation that the claimed nucleic acid be complementary to the nucleotide sequence at the stretch of at least ten consecutive nucleotides that is the same as in SEQ ID NOS 1-3, the structural limitations encompass any nucleic acid consisting of 10 to 300 nucleotides. The functional limitation is that the nucleic acid must be such that is hybridizes preferentially to RNA or DNA of bacteria A and not to non-bacteria A bacteria. Thus, claim 1 encompasses any nucleic acid that is 10 to 300 nucleotides in length and hybridizes preferentially to RNA or DNA of bacteria A and not to non-bacteria A bacteria.

Clearly if a nucleic acid hybridizes preferentially to RNA or DNA or bacteria and not to non-bacteria A bacteria, one skilled in the art would know how to use that nucleic acid based on the teachings in the specification. Thus, the specification teaches how to use all the nucleic acids encompassed by the claims. However, does the specification teach how to identify or make all nucleic acids that have both the structural limitation **and** the functional limitation? The answer in this case would be no since there is evidence sufficient to rebut the presumption that the full scope of claim 1 would be enabled without undue experimentation. Specifically, the state of the prior art as exemplified by Wallace et al and Sambrook et al is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. The database search results suggest that there are probes that would meet the structural limitations of the claims but not the functional limitation. The only specific guidance or working example given in the specification is for the three specific sequences of SEQ ID NOS 1-3 but there is no suggestion as to what the target sites in bacteria A are or what modifications can be made while retaining the functional limitation. The structural limitations of the claims clearly cover any nucleic acid that is 10 to 300 nucleotides in length (on the order of 4300 possible nucleic acids). Because of these considerations, one skilled in the art would have to make and test all nucleic acids that meet the structural limitations to determine which also meet the functional limitation. This amount of experimentation would be impossible in many lifetimes. Therefore, based on the empirical and unpredictable nature of the invention and state of the prior art, the limited guidance and working examples in the specification, and the extensive quantity of experimentation needed to identify the nucleic acids encompassed by the claims, it would be reasonable to conclude that it would require an undue amount of experimentation to identify the nucleic acids encompassed by the claims. In this case a scope rejection using form paragraph 7.31.03 would be appropriate.

The only issue remaining is the decision as to the scope that is enabled by the specification. Clearly the three probes used in the example are enabled. Is this all that is enabled? The answering of this question can be approached by considering claims having narrower scope, but still having written descriptive support, and determining whether the specification enables such a claim. Doing this, a claim of the following scope would be enabled on the facts presented here:

An isolated nucleic acid consisting of 10 to 35 nucleotides which hybridizes preferentially to RNA or DNA of bacteria A and not to non-bacteria A organisms, wherein said nucleic acid is or is complementary to a nucleotide sequence consisting of at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3.

Note, the upper limit of 35 nucleotides has clear descriptive support based on the fact that one of the specific probes of the example has 35 nucleotides. Nothing larger than 35, other than 300, has specific descriptive support and an upper limit of 300 would not be enabled for the reasons set forth above. The structural limitations of this claim would include approximately 800 different nucleic acids, some of which would not be expected to work in view of the state of the prior art. However, in view of the limited number of possibilities and the expectation that there are at least some, other than the specifically disclosed three, that would also meet the functional limitation, it would be reasonable to conclude that it would not require an undue amount of experimentation to identify the nucleic acids encompassed by the claim.

## Rejection:

Claims 1-3 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid consisting of 10 to 35 nucleotides which hybridizes preferentially to RNA or DNA of bacteria A and not to non-bacteria A organisms, wherein said nucleic acid is or is complementary to a nucleotide sequence consisting of at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3, does not reasonably provide enablement for any other embodiment encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to identify or make the invention commensurate in scope with these claims.

The specification discloses and the claims recite probes that hybridize preferentially to RNA or DNA of bacteria A but not to non-bacteria A organisms as well as methods of using the probes to detect bacteria A. However, the state of the prior art as exemplified by Wallace et al and Sambrook et al is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Furthermore, a database search was done for 10mers of the three specifically disclosed probes, the results of which are attached, which suggest that some of the probes encompassed by the structural limitations of the claims would not meet the functional limitation thereof. The only working example given in the specification is limited to the three specific sequences of SEQ ID NOS 1-3 and there is no suggestion as to what the target sites in bacteria A are or what modifications can be made while retaining the functional limitation. In addition, claim 1 recites three limitations on the nucleic acid, two structural and one functional. The two structural limitation are 1) that the nucleic acid consists of 10 to 300 nucleotides and 2) that the nucleic acid is or is complementary to a

nucleotide sequence **comprising** at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3. Since the nucleotide sequence mentioned merely **comprises** at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3, it encompasses any random sequence of any length as long as it has a stretch of at least ten consecutive nucleotides that is the same as in SEQ ID NOS 1-3. Furthermore, since there is no limitation that the claimed nucleic acid be complementary to the nucleotide sequence at the stretch of at least ten consecutive nucleotides that is the same as in SEQ ID NOS 1-3, the structural limitations encompass any nucleic acid consisting of 10 to 300 nucleotides. Thus, claim 1 encompasses any nucleic acid that is 10 to 300 nucleotides in length and hybridizes preferentially to RNA or DNA of bacteria A and not to non-bacteria A bacteria. Since the structural limitations of the claim clearly covers any nucleic acid that is 10 to 300 nucleotides in length (on the order of 4300 possible nucleic acids) and in view of the empirical and unpredictable nature of the art and lack of guidance with respect to appropriate modifications, one skilled in the art would have to make and test all nucleic acids that meet the structural limitations to determine which also meet the functional limitation. This amount of experimentation would be impossible in many lifetimes. Therefore, based on the empirical and unpredictable nature of the invention and state of the prior art, the limited guidance and working examples in the specification, and the extensive quantity of experimentation needed to identify the nucleic acids encompassed by the claims, it would require an undue amount of experimentation to identify or make the nucleic acids encompassed by the claims.

If claim 1 was limited as follows, this rejection would be overcome:

1. An isolated nucleic acid consisting of 10 to 35 nucleotides which hybridizes preferentially to RNA or DNA of bacteria A and not to non-bacteria A organisms, wherein said nucleic acid is or is complementary to a nucleotide sequence consisting of at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3.

# Example B: Hybridization Probes II

**Specification: THE ONLY DIFFERENCE BETWEEN THE FACTS IN EXAMPLE A AND THOSE OF EXAMPLE B IS THE LANGUAGE OF CLAIM 1** . Specifically, the specification discloses that bacteria A is known to cause a specific disease and, therefore, detection of bacteria A in a sample is desirable. The specification even discloses that methods are known which detect bacteria A in a sample via culturing techniques. According to the specification, such detection methods are difficult to perform and therefore detection methods using nucleic acid probes are preferred.

The specification discloses that one object of the invention is to provide nucleic acids complementary to unique nucleic acid sequences within the RNA or DNA of bacteria A and which can be used to detect bacteria A. Another object of the invention is to provide a method of detecting bacteria A in a sample by contacting the sample with a probe which preferentially hybridizes to RNA or DNA of bacteria A but not to non-bacteria A organisms.

The term "probe" is described in the specification as a nucleic acid between 10 and 300 base pairs in length which contain specific nucleotide sequences that specifically and preferentially hybridize under predetermined conditions to nucleic acid sequences of bacteria A. The probes optionally contain a detectable moiety.

The following three specific probes were disclosed:

Bacteria A probe 1 (35mer) (SEQ ID NO:1)

5'-CATTAGAGTC GTACGTGCTA GACTGATTAA CCGGT-3'

Bacteria A probe 2 (33mer) (SEQ ID NO:2)

5'-CAATCCAGTA AGTTTTACCC GGCCAAATAA AGG-3'

Bacteria A probe 3 (30mer) (SEQ ID NO:3)

5'-AAATAGCCAG ATCATTGCCC CGGACCCTTG-3'

An example appears in the specification which demonstrates how to carry out the detection and which shows that the three probes are specific for bacteria A and fail to hybridize to 50 other types of bacteria.

## Claims:

1. An isolated nucleic acid consisting of 10 to 300 nucleotides wherein said nucleic acid is or is complementary to a nucleotide sequence comprising any ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3.
2. A probe comprising a nucleic acid of claim 1 and a detectable moiety.
3. A method of detecting the presence of bacteria A in a sample suspected of containing bacteria A comprising
4. **a) contacting the sample with an isolated nucleic acid of claim 1,**
   **b) imposing hybridization conditions on the sample and said isolated nucleic acid to allow the formation of a hybridization product between said nucleic acid and RNA or DNA from bacteria A, if present in the sample, but not from RNA or DNA from non-bacteria A bacteria; and**
   **c) detecting any hybridization product as an indication of the presence of bacteria A in the sample.**

**State of the Prior Art:** Same as in Example A. Specifically, a search was carried out to compare the multitude of 10 nucleotide probes encompassed by the claims with sequences in the EMBL database with the following results:

**10,541 database hits for the 10mers of probe 1;**
**15,378 database hits for the 10mers of probe 2;**
**5,691 database hits for the 10mers of probe 3.**

Some of the hits for each probe were in the RNA or DNA of bacteria other than bacteria A, such as *Salmonella, Candida, and Streptococcus* .

Wallace et al, Methods Enzymol. 152:432-443 (1987).

Sambrook et al, Molecular Cloning, A Laboratory Manual , Second Edition, 1989, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, p. 11.47.

Wallace et al and Sambrook et al teach the empirical nature of determining the specificity of hybridization probes and the unpredictability of the effect of mismatches within an oligonucleotide probe.

The 50 different bacteria tested within the example in the specification are representative of bacteria in general.

## Analysis:

There is a demonstration in the specification that the three specifically disclosed probes can be used to detect bacteria A. Furthermore, the sequences of those probes are disclosed so that one skilled in the art could clearly make them. Therefore, the specification does teach how to make and use three embodiments encompassed by the claims. Accordingly, an objection/rejection using form paragraph 7.31.02 would be inappropriate. The issue is whether the enabled embodiments are representative of the scope of the claims.

Before this can be determined, the scope of at least claim 1 must be determined. Claim 1 recites two structural limitations for the nucleic acid which are 1) that the nucleic acid consist of 10 to 300 nucleotides and 2) that the nucleic acid is or is complementary to a nucleotide sequence **comprising** at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3. Since the nucleotide sequence mentioned merely **comprises** at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3, it encompasses any random sequence of any length as long as it has a stretch of at least ten consecutive nucleotides that is the same as in SEQ ID NOS 1-3. Furthermore, since there is no limitation that the claimed nucleic acid be complementary to the nucleotide sequence at the stretch of at least ten consecutive nucleotides that is the same as in SEQ ID NOS 1-3, claim 1 encompasses any nucleic acid that is 10 to 300 nucleotides in length.

Since all nucleic acids within the scope of claim 1 could be clearly identified and since nucleic acids can readily be synthesized by those skilled in the art, one skilled in the art would know how to identify and make all the nucleic acids encompassed by claim 1. However, does the specification teach how to use all nucleic acids encompassed by claim 1? The answer in this case would be no. The only disclosed use for the nucleic acids is in a method of detecting the presence of bacteria A in a sample by preferentially hybridizing to RNA or DNA of bacteria A but not to non-bacteria A organisms, as in claim 3. The state of the prior art as exemplified by Wallace et al and Sambrook et al is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. The database search results suggest that there are probes that would meet the limitations of the claims but would not function to detect bacteria A by preferentially hybridizing to RNA or DNA of bacteria A but not to non-bacteria A organisms. The only specific guidance or working example given in the specification is for the three specific sequences of SEQ ID NOS 1-3 but there is no suggestion

as to what the target sites in bacteria A are or what modifications can be made while retaining the ability to preferentially hybridize to RNA or DNA of bacteria A. Therefore, based on these considerations, it would be reasonable to conclude that it would require an undue amount of experimentation to determine how to use all the nucleic acids encompassed by the claims for detecting bacteria A in a sample. In this case a scope rejection using form paragraph 7.31.03 would be appropriate.

The only issue remaining is the decision as to the scope that is enabled by the specification. Clearly the three probes used in the example are enabled. Is this all that is enabled? The answering of this question can be approached by considering claims having narrower scope, but still having written descriptive support, and determining whether the specification enables such a claim. Doing this, a claim of the following scope would be enabled on the facts presented here:

An isolated nucleic acid consisting of 10 to 35 nucleotides which hybridizes preferentially to RNA or DNA of bacteria A and not to non-bacteria A organisms, wherein said nucleic acid is or is complementary to a nucleotide sequence consisting of at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3.

Note, the insertion of the functional limitation, i.e., that the nucleic acid must hybridize preferentially to RNA or DNA or bacteria A and not to non-bacteria A organisms, by itself would be such that the disclosure would enable the use of those nucleic acids encompassed by the claim. However, there would still be enablement problems, as seen in Example A, requiring further structural limitations. The upper limit of 35 nucleotides has clear descriptive support based on the fact that one of the specific probes of the example has 35 nucleotides. Nothing larger than 35, other than 300, has specific descriptive support and an upper limit of 300 would not be enabled for the reasons set forth above and in Example A. The structural limitations of this claim would include approximately 800 different nucleic acids, some of which would not be expected to work in view of the state of the prior art. However, in view of the limited number of possibilities and the expectation that there are at least some, other than the specifically disclosed three, that would also meet the functional limitation, it would be reasonable to conclude that it would not require an undue amount of experimentation to identify and use the nucleic acids encompassed by the claim.

## Rejection:

Claims 1-3 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the exact probes represented by SEQ ID NOS 1-3 and 10mers to 35mers thereof that preferentially hybridize to RNA or DNA of bacteria A and not to non-bacteria A organisms, does not reasonably provide enablement for any other embodiment encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification discloses and the claims recite probes having 10 to 300 nucleotides as well as methods of using the probes to detect bacteria A. However, the state of the prior art as exemplified by Wallace et al and Sambrook et al is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Furthermore, a database

search was done for 10mers of the three specifically disclosed probes, the results of which are attached, which suggest that some of the probes encompassed by the claims would not preferentially hybridize to RNA or DNA of bacteria A and not to non-bacteria A organisms so as to detect bacteria A. The only working example given in the specification is limited to the three specific sequences of SEQ ID NOS 1-3 and there is no suggestion as to what the target sites in bacteria A are or what modifications can be made to the sequences or the hybridization conditions while retaining the ability to detect bacteria A. In addition, claim 1 recites two limitations on the nucleic acids, both structural. The two structural limitations are 1) that the nucleic acid consists of 10 to 300 nucleotides and 2) that the nucleic acid is or is complementary to a nucleotide sequence **comprising** at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3. Since the nucleotide sequence mentioned merely **comprises** at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3, it encompasses any random sequence of any length as long as it has a stretch of at least ten consecutive nucleotides that is the same as in SEQ ID NOS 1-3. Furthermore, since there is no limitation that the claimed nucleic acid be complementary to the nucleotide sequence at the stretch of at least ten consecutive nucleotides that is the same as in SEQ ID NOS 1-3, claim 1 encompasses any nucleic acid that is 10 to 300 nucleotides in length (on the order of 4300 possible nucleic acids). In view of this, the empirical and unpredictable nature of the art, the lack of guidance with respect to appropriate modifications and the lack of guidance as to how to use other probes within the scope of the claims to detect bacteria A, the specification does not teach one skilled in the art how to successfully use probes of the claimed scope without undue experimentation.

If claim 1 was limited as follows, this rejection would be overcome:

1. An isolated nucleic acid consisting of 10 to 35 nucleotides which hybridizes preferentially to RNA or DNA of bacteria A and not to non-bacteria A organisms, wherein said nucleic acid is or is complementary to a nucleotide sequence consisting of at least ten consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS 1, 2, and 3.

# Example C: Chemical Reagents I

**Specification:** The specification discloses that prothrombin is essential to the blood coagulation cascade and that a deficiency in prothrombin in blood leads to the hemorrhagic disease known as congenital hypoprothrombinemia. Thus, the object of the invention, as set forth in the specification, is to provide a method and reagent for detecting prothrombin in blood, wherein the method can be used in the diagnosis of congenital hypoprothrombinemia. If the results of the method indicate that prothrombin is present in normal amounts in the patient's blood sample then congenital hypoprothrombinemia is ruled out, whereas if the results of the method indicate that the patient's blood is deficient in prothrombin then the patient is diagnosed as having congenital hypoprothrombinemia and is treated accordingly. The specification discloses that treatments for that condition are well known in the art. The normal range for prothrombin in blood is also well known in the art and is listed in the specification. The specification discloses that when the well known material compound X is added to whole blood, it reacts with prothrombin to produce an absorbance change when measured at 280nm. However, the specification discloses that fibrinogen in blood also reacted with compound X to interfere with the results. To overcome

this, the specification discloses adding boric acid to the blood along with compound X. The boric acid complexes with the fibrinogen to inhibit any reaction of the fibrinogen and compound X so that any absorbance change would be due solely to prothrombin. The specification includes a general statement that any other compound which inhibits the reaction of fibrinogen with compound X can be used in place of the boric acid but nothing other than boric acid is specifically named and no guidance is provided as to how or why the boric acid complexes with fibrinogen to inhibit its reaction with compound X. The specification discloses appropriate concentration ranges for compound X and boric acid as well as the appropriate mixing ratios for the reagent and sample but states that the ranges and ratios are not critical. The sole example in the specification carries out the method by adding a predetermined amount of the reagent to a whole blood sample, measuring the absorbance of the whole blood sample at 280nm before and after the addition of the reagent, calculating the difference between the absorbance of the whole blood sample before and after the addition of the reagent, and determining the amount of prothrombin in the sample from the difference. The example uses a reagent containing compound X and boric acid in specific amounts. The example also demonstrates how to establish the appropriate calibration curve.

## Claims:

1. A reagent for measuring the amount of prothrombin in whole blood comprising compound X and a substance which inhibits any reaction between fibrinogen and compound X.
2. A method for measuring the amount of prothrombin in whole blood comprising:
   adding a predetermined amount of the reagent of claim 1 to a whole blood sample;
   measuring the absorbance of the whole blood sample at 280nm before and after the addition of the reagent;
   calculating the difference between the absorbance of the whole blood sample before and after the addition of the reagent; and
   determining the amount of prothrombin in the sample from the difference.
3. 3. A reagent according to claim 1 wherein the substance is boric acid.

**State of the Prior Art:** No compounds which inhibit any reaction between fibrinogen and compound X are known.

## Analysis:

There is a demonstration that one reagent, i.e., one that contains compound X and boric acid, can be used to detect prothrombin. Furthermore, since compound X and boric acid are well known materials, one skilled in the art could clearly make them without undue experimentation. Therefore, the specification does teach how to make and use one embodiment encompassed by the claims, particularly the embodiment recited in claim 3. Accordingly, an objection/rejection using form paragraph 7.31.02 would be inappropriate. The issue is whether the enabled embodiment is representative of the scope of the claims. Based on the undue experimentation factors, particularly the breadth of the claims and the lack of guidance as to other materials which inhibit any reaction between compound X and fibrinogen, the conclusion would be that the enabled embodiment is not representative of the scope of claims 1-2. Therefore, a scope rejection using form paragraph 7.31.03 would be appropriate against claims 1-2.

## Rejection:

Claims 1-2 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a reagent that includes compound X and boric acid, does not reasonably provide enablement for reagents that include compound X and any substance which inhibits any reaction between fibrinogen and compound X. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims recite a reagent and a method of using the reagent to detect prothrombin wherein the reagent includes a substance which inhibits any reaction between compound X and fibrinogen. This encompasses any substance which has that ability. However, the specification only teaches the use of boric acid as the inhibitor. The specification does not provide guidance as to any other substances which have that ability nor does the specification disclose specific characteristics for such substances. Furthermore, the specification fails to provide guidance as to how or why the boric acid complexes with fibrinogen to inhibit its reaction with compound X. Without such information, one skilled in the art could not predict which substances out of the vast numbers of known substances would react with fibrinogen in a manner similar to boric acid and, accordingly, one skilled in the art would be required to perform undue experimentation to identify any other compounds that would complex with fibrinogen so as to inhibit its reaction with compound X. Therefore, one skilled in the art could not make the invention without undue experimentation.

**Modifications to the Above Facts:** Let us assume that the above noted application was filed on January 11, 1994. Subsequent to that date, two articles were published in Nature, one on March 26, 1995 and one on October 10, 1995, each of which discloses five different compounds which inhibit any reaction between fibrinogen and compound X. Another original application, identical to the above application, is filed on July 20, 1996. Does the enablement analysis above change with respect to this later filed application? Clearly the answer is yes. Since the specification suggests the use of compounds other than boric acid, such other compounds are well known in the prior art as exemplified by the two articles, and the specification need not disclose what is well known in the art, and preferably omits it, all of the claims in the July 20, 1996 application would be enabled.

# Example D: Chemical Reagents II

**Specification: THE MAJOR DIFFERENCES BETWEEN THE FACTS OF EXAMPLE C AND THOSE OF EXAMPLE D ARE: 1) IN EXAMPLE C, BORIC ACID IS DISCLOSED AS THE INHIBITOR SUBSTANCE WHEREAS NO SPECIFIC INHIBITOR SUBSTANCE IS DISCLOSED IN EXAMPLE D; THERE ARE NO WORKING EXAMPLES IN EXAMPLE D; AND 3) EXAMPLE C HAS THREE CLAIMS WHEREAS EXAMPLE D HAS TWO CLAIMS.**

Specifically, the specification discloses that prothrombin is essential to the blood coagulation cascade and that a deficiency in prothrombin in blood leads to the hemorrhagic disease known as congenital hypoprothrombinemia. Thus, the object of the invention, as set forth in the specification, is to provide a method and reagent for detecting prothrombin in blood, wherein the method can be used in the diagnosis of congenital hypoprothrombinemia. If the results of the method indicate that prothrombin is

present in normal amounts in the patient's blood sample then congenital hypoprothrombinemia is ruled out, whereas if the results of the method indicate that the patient's blood is deficient in prothrombin then the patient is diagnosed as having congenital hypoprothrombinemia and is treated accordingly. The specification discloses that treatments for that condition are well known in the art. The normal range for prothrombin in blood is also well known in the art and is listed in the specification. The specification discloses that when the well known material compound X is added to whole blood, it reacts with prothrombin to produce an absorbance change when measured at 280nm. However, the specification discloses that fibrinogen in blood also reacts with compound X to interfere with the results. To overcome this, the specification discloses adding an inhibitor substance to the blood along with compound X. The inhibitor substance is to complex with the fibrinogen to inhibit any reaction of the fibrinogen and compound X so that an absorbance change would be due solely to prothrombin. The specification includes a general statement that any compound which inhibits the reaction of fibrinogen with compound X can be used. However, not one specific inhibitor is mentioned in the specification. The specification discloses appropriate concentration ranges for compound X as well as the appropriate mixing ratios for the reagent and sample but states that the ranges and ratios are not critical. There is no working example but the specification does clearly disclose that the method would be carried out by adding a predetermined amount of the reagent to a whole blood sample, measuring the absorbance of the whole blood sample at 280nm before and after the addition of the reagent, calculating the difference between the absorbance of the whole blood sample before and after the addition of the reagent, and determining the amount of prothrombin in the sample from the difference.

## Claims:

1. A reagent for measuring the amount of prothrombin in whole blood comprising compound X and a substance which inhibits any reaction between fibrinogen and compound X.
2. A method for measuring the amount of prothrombin in whole blood comprising:
   adding a predetermined amount of the reagent of claim 1 to a whole blood sample;
   measuring the absorbance of the whole blood sample at 280nm before and after the addition of the reagent;
   calculating the difference between the absorbance of the whole blood sample before and after the addition of the reagent; and
   determining the amount of prothrombin in the sample from the difference.

**State of the Prior Art:** No compounds which inhibit any reaction between fibrinogen and compound X are known.

## Analysis:

The claims require a substance which inhibits any reaction between compound X and fibrinogen. However, the specification fails to disclose any specific substance that has that ability and there is no working example to provide this missing information. Therefore, based on the undue experimentation factors, particularly the breadth of the claims, the lack of guidance as to materials which inhibit any

reaction between compound X and fibrinogen, and the lack of working examples, the conclusion would be that the specification does not teach how to make and use even one embodiment encompassed by the claims. Accordingly, an objection/rejection using form paragraph 7.31.02 would be appropriate.

### Rejection:

Claims 1-2 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

The claims recite a reagent and a method of using the reagent to detect prothrombin wherein the reagent includes a substance which inhibits any reaction between compound X and fibrinogen. This encompasses any substance which has that ability. However, the specification does not provide guidance as to any specific substances which have that ability nor does the specification disclose specific characteristics for such substances. Furthermore, the specification fails to provide guidance as to how any inhibitor substance should complex with fibrinogen to inhibit its reaction with compound X. No working examples are provided to provide such missing information. Without such information, one skilled in the art could not predict which substances out of the vast numbers of known substances would react with fibrinogen in the manner required by the method and, accordingly, one skilled in the art would be required to perform undue experimentation to identify any compounds that would complex with fibrinogen so as to inhibit its reaction with compound X. Therefore, one skilled in the art could not make the invention without undue experimentation.

## Example 5E: Peptides for Treating Obesity

**Specification:** The specification discloses an anti-obesity peptide having the following amino acid sequence:

1 5 10 15

Phe Ile Gly His Thr Ser Xaa Thr His Glu Xaa Phe Ala Thr Xaa Trp Glu Leu Leu (SEQ ID NO 1).

Where:

Xaa at position 7 is Gln, Ile, or Met;
Xaa at position 11 is Asp, Gln, or Glu; and
Xaa at position 15 is Ser or Pro.

Preferably,

Xaa at position 7 is Ile;
Xaa at position 11 is Glu; and
Xaa at position 15 is Ser.

The specification also discloses a pharmaceutical formulation comprising the peptide of SEQ ID NO 1 and a pharmaceutically acceptable carrier, diluent, and/or excipient, as well as a method of treating obesity by administering the peptide of SEQ ID NO 1 to an obese mammal, such as mice or humans. Several routes of administration are disclosed but no dosages, not even general ranges, are disclosed.

The specification states that the peptide can be made by recombinant DNA technology or well known peptide synthesis procedures. Furthermore, the specification lists DNA sequences, vectors, host cells, and isolation techniques suitable for producing the peptide by recombinant DNA technology as well as specific peptide synthesis techniques suitable for producing the peptide.

The application discloses but does not exemplify that the peptide is a fragment of a larger protein produced in adipose tissue. The application also discloses but does not exemplify that the peptide is able to control body weight gain in normal and obese subjects. The specification discloses that suitable test animals include normal mice and obese mice, especially the ob/ob mouse model of obesity and diabetes, which is disclosed as being generally accepted in the art as being indicative of the obesity condition. The specification discloses how to carry out the animal model tests but fails to disclose whether such tests were done using the peptide of the invention. The specification also goes on to state that the peptide is also useful in the production of antibodies for diagnostic use and, as a peptide, is useful as feed additives for animals.

## Claims:

1. 1. A peptide consisting of the sequence

1. 1 5 10 15

   Phe Ile Gly His Thr Ser Xaa Thr His Glu Xaa Phe Ala Thr Xaa Trp Glu Leu Leu (SEQ ID No. 1), wherein

   Xaa at position 7 is Gln, Ile, or Met;
   Xaa at position 11 is Asp, Gln, or Glu; and
   Xaa at position 15 is Ser or Pro.

2. The peptide of claim 1 wherein Xaa at position 7 is Ile; Xaa at position 11 is Glu; and Xaa at position 15 is Ser.
3. A pharmaceutical composition comprising the peptide of claim 1 and a pharmaceutically acceptable carrier.
4. A pharmaceutical composition comprising the peptide of claim 2 and a pharmaceutically acceptable carrier.
5. A method of treating obesity, which comprises administering to a mammal in need thereof the peptide of claim 1.
6. A method of treating obesity, which comprises administering to a mammal in need thereof the peptide of claim 2.

**State of the Prior Art:** There are no structurally similar peptides known in the art for treating obesity. There are other proteins that the art suggests play a role in obesity. The following references establish the state of the art with respect to such proteins.

Zhang et al, Nature, Vol. 372, pp. 425-432, December 1994.

Rink, Nature, Vol. 372, pp. 406-407, December 1994.

Marx, Science, Vol. 266, pp. 1477-1478, December 1994.

It is well established in the art how to use proteins and peptides as additives in animal feed.

## Analysis:

The specification clearly teaches how to make all the peptides and compositions encompassed by the claims. Therefore, "how to make" is not an issue with any of the claims.

With respect to claims 1-2, the fact that the specification discloses that the peptides can be used as an additive to animal feed in combination with the fact that it is well established in the art how to use proteins and peptides as additives in animal feed leads to a conclusion that the specification also teaches how to use the entire scope of peptides recited in claims 1-2. Since no specific use is recited in these claims, one enabled use that covers the full scope of the claims is sufficient to preclude an enablement rejection of a compound claim based on the failure to teach "how to use".

With respect to claims 3-4, the "pharmaceutical" and "pharmaceutically acceptable carrier" language in combination with the fact that the only disclosed pharmaceutical use of the compositions is for treating obesity leads to the conclusion that these claims should be evaluated in terms of whether the specification teaches how to use the compositions for treating obesity. Since method claims 5-6 must be evaluated in terms of the recited use, treating obesity, claims 3-6 should be evaluated together. In this case, the art noted above teaches that few medical problems have proved to be more intractable than obesity (Marx). Furthermore, even though other proteins are suggested as playing a role in obesity (Zhang), the art, such as Rink and Marx, suggest that it is not even known how to use these proteins for treating obesity. This state of the prior art suggests a lack of predictability in this art which, taken with the fact that there is a lack of guidance with respect to dosages and a lack of working examples, leads to the conclusion that it would require undue experimentation to use the invention of claims 3-6. With respect to claims 3-4, it is also noted that if the "pharmaceutical" and "pharmaceutically acceptable" language was deleted from the claims, the analysis would be the same as that set forth above with respect to claims 1-2. Therefore, an enablement rejection using form paragraph 7.31.02 of claims 3-6 would be appropriate along with a suggestion to remove the "pharmaceutical" and "pharmaceutically acceptable" language from claims 3-4 to overcome the rejection with respect to these claims.

## Rejection:

Claims 3-6 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertain, or with which it is most nearly connected, to use the invention.

Claims 3-6 recite pharmaceutical compositions and methods of treating obesity using certain specific peptides. However, the specification fails to disclose any dosages for use in treating obesity. Furthermore, while the specification sets forth tests for assay anti-obesity activity of the peptides, the specification fails to provide any indication that such tests were done. Therefore, the specification also fails to provide any working examples. Marx states that few "medical problems have proved to be more intractable than obesity" and even though other proteins are suggested as playing a role in obesity (Zhang), the art, such as Rink and Marx, suggest that it is not even known how to use these proteins for treating obesity and that there is much more to be done before obesity can be treated using such proteins. In view of the intractable nature and unpredictability of treating obesity and the lack of guidance with respect to dosages and the lack of working examples, one skilled in the art could not use the inventions of claims 3-6 without undue experimentation. Note, removing "pharmaceutical" and "pharmaceutically acceptable" from claims 3-4 would overcome the rejection of these claims since one would know how to use such compositions as additives in animal feed as disclosed in the specification.

**Modifications to the Above Facts:** Let us assume that in addition to the above facts, the specification actually stated "The disclosed animal model assays were carried out using the peptides of the invention and the peptides were active in at least one of the assays. Therefore, the peptides are useful in treating obesity and those disorders implicated by obesity." Does this change the analysis set forth above? For claims 1-2, the answer is no. For claims 3-6, the answer is yes. Specifically, if the assays are reasonably correlative to treatment in other mammals such a statement would constitute the presence of working examples, even without the specific data. In this case, since specific dosages are not disclosed generally or in the examples, the only issue remaining is whether it would require an undue amount of experimentation to determine the proper dosages based on the examples and the state of the prior art and any enablement rejection must address this issue. If the assays do not reasonably correlate to treatment in other mammals based on the state of the art, this issue would have to be raised along with the other issues noted in the analysis and rejection above.

Note, taking the position that the assays are reasonably correlative to treatment in other mammals, it is proper to accept as being true the statement that the peptides were active in the assays, even in the absence of specific data. The Office must accept as being true the statements supporting enablement unless there is an objective reason, usually supported with documentary evidence, to question them, i.e., the burden is on the Office to demonstrate that there is an objective reason, usually supported by documentary evidence, to question the statement. Here, there is no evidence indicating that the peptides were not active in the assays. However, this analysis does not necessarily apply to other issues, such as a showing of unexpected results so as to overcome a rejection under 35 U.S.C. 103. In that case, a statement that the assays demonstrated unexpected results for the inventive peptides, in the absence of the specific results, would not be persuasive since it is applicant's burden to rebut the prima facie case of obviousness and the Office cannot determine whether applicant has met that burden without the results being present.

# Example F: Enablement and Prior Art Rejections

**Specification:** Compounds of the formula I or a pharmaceutically acceptable salt thereof are disclosed:

I wherein R1 is C1 - C10 alkyl; R2 and R3 are independently hydrogen, methyl, methoxy, fluoro, chloro, bromo, or trifluoromethyl;


Chemical Structure 1

Z is


Chemical Structure 2

or


Chemical Structure 3

; and Het is an heteroaromatic group.

The compounds are said to possess efficacy in treating a wide range of tumors in mammals. No antitumor data ( *in vitro* or *in vivo* ) are presented in the specification. The tumor types are merely listed and include estrogen-dependent tumors such as breast cancer. Detailed methods of synthesizing the compounds are disclosed.

## Claim:

1. A method of treating tumors in mammals which comprises administering to a mammal in need thereof an antitumor effective amount of the compound of formula I or a pharmaceutically acceptable salt thereof.

**State of the Prior Art:** The following references are representative of the state of the prior art:
U.S. Patent No. 4,605,661
U.S. Patent No. 4,916,144

These two patents disclose compounds which are effective against estrogen dependent tumors and which are stucturally similar to some of the compounds recited in claim 1.

Internal Medicine, 4th Edition, Editor-in-Chief Jay Stein, Chapters 71-72, pages 699-715. This reference provides evidence that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocol.

## Situation 1 - Proper §112, ¶1 and §103 rejections in the same Office action:

Claim 1 is rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for treatment of estrogen dependent tumors with compounds of formula I wherein Het is imidazolyl, does not reasonably provide enablement for treatment of tumors generally with all of the compounds of the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with claim 1.

The cancer therapy art remains highly unpredictable, and no example exists for efficacy of a single product against tumors generally. Specifically, Internal Medicine, 4th Edition, Editor-in-Chief Jay Stein, Chapters 71-72, pages 699-715, teaches that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocol. It is also known that certain tumors are dependent upon estrogen for their induction or stimulation (e.g. breast tumors) and others are not. See USPs 4605661 and 4916144. Based on this state of the art, an estrogen inhibitor would be expected to be effective against those that are dependent upon estrogen for their induction, but not against those that do not depend upon estrogen for their induction. Since, the compounds used in claim 1 are structurally related to compounds known to be effective against estrogen dependent tumors (again see USPs 4605661 and 4916144), one skilled in the art would expect the compounds used in claim 1 in which Het is imidazolyl to have similar activity and, accordingly, would know how to make and use these compounds for treating estrogen dependent tumors. However, when Het is not imidazolyl, the compounds would not be expected to be estrogen inhibitors due to stuctural differences. Furthermore, applicant has provided no guidance or working examples teaching one skilled in the art how to determine which of the countless products used in claim 1 would be effective against which tumors. As evidenced by the references noted above, one would not expect all of the compounds of formula I to be effective against all tumors. Therefore, based on the unpredictable nature of the invention and state of the prior art, the lack of guidance and working examples, and the extreme breadth of the claims, one skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

Claim 1 is rejected under 35 U.S.C. 103 as obvious over Hirsch et al (USP 4605661). Hirsch et al discloses (see example 3 at column 4)


Chemical Structure 4

which differs from a compound within instant formula I by hydrogen vs. alkyl substitution at position 2. The reference compound inhibits aromatase and is useful for treating breast cancer. See Table I at top of column 5. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a methyl group for hydrogen in the reference compound. One would have been motivated to make the substitution because of the close structural relationship of the two compounds (ethyl and isopropyl are homologs) and because one of ordinary skill in the art would have reasonably expected that such substitution would produce an aromatase inhibitor useful for treating breast cancer in view of that close structural relationship.

## Situation 2 - Improper §112, ¶1 and §103 rejections in the same Office action:

Claim 1 is rejected under 35 U.S.C. 112, first paragraph because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The cancer therapy art remains highly unpredictable, and no example exists for efficacy of a single product against tumors generally. Specifically, Internal Medicine, 4th Edition, Editor-in-Chief Jay Stein, Chapters 71-72, pages 699-715, teaches that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocol. Furthermore, applicant has provided no guidance or working examples teaching one skilled in the art how to determine which of the countless products used in claim 1 would be effective against which tumors. As evidenced by the reference noted above, one would not expect all of the compounds of formula I to be effective against all tumors. Therefore, based on the unpredictable nature of the invention and state of the prior art, the lack of guidance and working examples, and the extreme breadth of the claims, one skilled in the art could not use the claimed invention without undue experimentation.

Claim 1 is rejected under 35 U.S.C. 103 as obvious over Hirsch et al (USP 4605661). Hirsch et al discloses (see example 3 at column 4)


Chemical Structure 4

which differs from a compound within instant formula I by hydrogen vs. alkyl substitution at position 2. The reference compound inhibits aromatase and is useful for treating breast cancer. See Table I at top of column 5. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a methyl group for hydrogen in the reference compound. One would have been motivated to make the substitution because of the close structural relationship of the two compounds (ethyl and isopropyl are homologs) and because one of ordinary skill in the art would have reasonably expected that such substitution would produce an aromatase inhibitor useful for treating breast cancer in view of that close structural relationship.

## Analysis:

Based on the state of the prior art considered with the disclosure, some of the compounds within the claimed genus (or close structural analogs thereof) are useful for treating estrogen-dependent tumors. There is no reason to question enablement for those compounds because of their structural similarity to known compounds which have the same use, i.e., treating estrogen-dependent tumors. Accordingly, the scope rejection in situation 1 is appropriate. Since something is clearly enabled for these reasons, the enablement rejection in situation 2, which states that nothing is enabled, is inappropriate.

The obviousness rejection is appropriate in both situations because certain compounds within the disclosed genus would have been obvious for the reference use (which also happens to be the instant utility). Since both rejections are appropriate in situation 1, making both rejections would be proper. However, in situation 2, the combination of rejections is inconsistent because it implies that one skilled in the art would be able to make the claimed analogs of the prior art and know how to use them (the §103 rejection), but at the same time would not know how to use any of the compounds of the instant invention (the §112 rejection). This is not proper given the facts of this case.

**Modification of the Above Facts:** Let us assume now that the specification did not list any tumor types for which the compounds possess efficacy. Does this change the analysis set forth above? The answer is no. In this case, situation 1 would still be appropriate. However, applicant should also be put on notice that the enabled embodiment lacks explicit written descriptive support in the specification as filed.

# Example G: Gene Therapy

**Specification:**The specification discloses that viruses are commonly used as vectors to introduce genes into cells by first inserting the gene of interest into the DNA of the virus and then contacting the virus with the cells. The virus then infects the cells through cell binding receptors on the surface of the virus which bind to the cells and cause the virus to be internalized by the cells. Once internalized, the virus inserts its DNA, including the gene of interest, into the genome of the cell in such a manner that the gene of interest is expressed so as to produce its corresponding protein. Applicant has discovered that if viral vectors are first contacted with the recently discovered protein algernin, the algernin complexes with the cell binding receptors on the surface of the virus, changes the conformation thereof, and increases the infectivity of the viral vector by a factor of ten. Thus, the invention relates to a complex between a viral vector and algernin and is applicable to all situations where it is desirable to introduce genes into mammalian cells with a viral vector with a higher than normal rate of infectivity. Specifically, the specification discloses that the modified viral vector can be used*in vitro*for providing desired biological action in the cells, e.g., to produce useful proteins, and, when combined with a pharmaceutically acceptable carrier in a pharmaceutical composition,*in vivo*for medicinal purposes, such as gene therapy.
The specification lists several examples of viral vectors which are candidates for use within the claimed invention. The specification also provides the amino acid sequence of algernin as well as various methods of obtaining algernin suitable for use in the invention.

The specification includes several *in vitro* working examples with representative samples of viral vectors, genes of interest, and cells demonstrating that when the viral vectors are complexed with algernin, the complex shows a higher rate of infectivity. The examples further demonstrate that the gene of interest in the infected cells is then expressed so as to produce its corresponding protein. The specification does not show any examples relating to gene therapy or any *in vivo* use of the viral vectors.

## Claims:

1. A viral vector comprising:
   a virus comprising a cell binding receptor on the surface thereof
   and a gene of interest, not normally present in the virus, inserted

within the DNA of the virus; and
algernin complexed to the cell binding receptor of the virus.

2. A pharmaceutical composition comprising a therapeutically effective amount of the complex of claim 1 and a pharmaceutically acceptable carrier.
3. A method for introducing a gene of interest into a cell comprising contacting said cell with the viral vector of claim 1.

**State of the Prior Art:** The state of the prior art is such that using viral vectors to insert genes into cells *in vitro* is well known and is used in applications such as protein production and as a research tool.

Orkin et al., December 7, 1995, "Report and Recommendation of the Panel to Assess the NIH Investmen in Research on Gene Therapy", issued by the National Institutes of Health - This reference teaches that using viral vectors to insert genes into cells *in vivo* for therapeutic purposes, i.e., gene therapy, is highly unpredictable and undeveloped in view of the complexity of *in vivo* systems.

## Analysis:

The specification discloses an*in vitro*use for the viral vector of claim 1 and clearly discloses how to make and use the viral vector in the*in vitro*environment. Since claim 1 does not recite any environment of use, only one enabled use covering the scope of the claim is needed to enable the claim. Therefore, the disclosure with respect to the*in vitro*use of the viral vector is sufficient to enable claim 1 and it would be inappropriate to include claim 1 in a rejection under 35 U.S.C. 112, first paragraph.
With respect to claim 2, the "pharmaceutical composition", "therapeutically effective", and "pharmaceutically acceptable carrier" language in combination with the fact that the only disclosed pharmaceutical use of the compositions is for gene therapy leads to the conclusion that this claim should be evaluated in terms of whether the specification teaches how to make and use the composition for gene therapy. Since the specification fails to provide any guidance regarding gene therapy, such as dosages, routes of administration, and working examples, and the state of the prior art is such that gene therapy is unpredictable and undeveloped, it would be reasonable to conclude that it would require an undue amount of experimentation to determine the therapeutically effective amounts and use the compositions for gene therapy. For the reasons set forth above with respect to claim 1, it is clear that non-therapeutic compositions would be enabled. Since some compositions are enabled, it would be best to make a scope rejection of claim 2 using form paragraph 7.31.03.

Claim 3 is a broad claim. When read in light of the specification, it covers *in vitro* applications as well as *in vivo* gene therapy applications. Thus, claim 3 must be evaluated as to whether the specification enables the entire scope of the claim. From the above discussion with respect to claims 1 and 2, it is clear that the specification enables the *in vitro* aspects of the claim but not the *in vivo* gene therapy aspects of the claim. Therefore, it would be reasonable to make a scope rejection of claim 3 using form paragraph 7.31.03.

## Rejection:

Claims 2-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabled for non-therapeutic compositions and*in vitro*uses of the viral vector of the invention, does not reasonably provide enablement for pharmaceutical compositions and their use*in vivo*for gene therapy. The

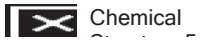
specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
Claim 2 is directed to a pharmaceutical composition comprising a specific viral vector, the only disclosed use of the composition being *in vivo* gene therapy. Claim 3 is directed to a method which encompasses of using the specific viral vector for *in vivo* gene therapy. However, the specification fails to adequately teach how to make the composition having a "therapeutically effective amount" of the viral vector and how to use the composition and vector for *in vivo* gene therapy. Gene therapy is a highly unpredictable and undeveloped field and the skill in the art is high. See Orkin et al. which states:

2. While the expectations and the promise of gene therapy are great, clinical efficacy has not be definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.
3. Significant problems remain in all basic aspects of gene therapy.
The specification fails to disclose the intended patients, amounts of the viral vector to be administered, what amount is considered to be therapeutically effective, the route and time course of administration, the sites of administration, the intended therapeutic product, the intended disease, and the intended target organs. The specification also lacks any working examples showing that the viral vector as claimed would deliver the genes encoding the therapeutic products to the appropriate site and that the genes once delivered would be expressed sufficiently to provide adequate product to effect the desired therapy. In view of the quantity of experimentation necessary to determine the above parameters, the lack of direction or guidance presented, the absence of working examples for *in vivo* gene therapy, the breadth of the claims, and the unpredictable and undeveloped state of the art with respect to gene therapy, it would require undue experimentation for one skilled in the art to practice the entire scope of the claimed invention.

If claims 2 and 3 were limited as follows, this rejection would be overcome:
2. A composition comprising the viral vector of claim 1 and a carrier.
3. A method for introducing a gene of interest into a cell *in vitro* comprising contacting said cell with the viral vector of claim 1.

# Example H: Endothelin Receptor Antagonists

**Specification:**The specification discloses compounds of formula




wherein HET is a 5- or 6-membered heterocyclic ring containing at least one hetero atom selected from N, S and O, such as morpholinyl, piperazinyl, piperidinyl, pyrazinyl, pyrimidinyl, oxadiazolyl, thiadiazolyl, oxazolyl, and thiazolyl, wherein HET can be optionally substituted with X; X is hydrogen, lower alkyl, lower alkoxy, hydroxy, halo, lower monoalkylamino, lower dialkylamino, nitro, cyano, acylamino, aminocarbonyl, or formyl; and pharmaceutically acceptable salts thereof. The specification also discloses that these compounds are endothelin receptor antagonists useful in treatment of all endothelin (ET)-related disorders. A laundry list of diseases to be treated is disclosed, e.g., hypertension, renal, glomerular, or

mesangial cell disorders, endotoxemia, and ischemia. Dosages of 0.1-100 mg/Kg/day are disclosed. Three compounds are prepared. No administration protocol is disclosed nor are there any examples ( *in vitro* or *in vivo* ) demonstrating the use of any of the compounds.

## Claims:

1. A compound of formula

1.  Chemical Structure 5

   or a pharmaceutical acceptable salt thereof, wherein HET is a 5- or 6-membered heterocyclic ring containing at least one hetero atom selected from N, S and O, and wherein HET is optionally substituted with X; and X is hydrogen, lower alkyl, lower alkoxy, hydroxy, halo, lower monoalkylamino, lower dialkylamino, nitro, cyano, acylamino, aminocarbonyl, formyl; with the proviso that HET is not 3,4-dimethyl-5-isoxazolyl.

2. A method of treating endothelin-related disorders in a mammal, which comprises administering to said mammal an effective amount of a compound of claim 1.
3. A method of treating hypertension, which comprises administering an effective amount of a compound of Claim 1.
4. A method of treating renal, glomerular or mesangial cell disorders, which comprises administering an effective amount of a compound of Claim 1.
5. A method of treating endotoxemia, which comprises administering an effective amount of a compound of claim 1.
6. A method of treating ischemia, which comprises administering an effective amount of a compound of claim 1.

## State of the prior art:

Doherty, Journal of Medicinal Chemistry, Vol. 35, No. 9, 1493-1508 (1992). The Doherty article, last page, clearly evidences that work in the field of ET receptor antagonism is only in the investigational stages, the possibility for the need of selectivity towards various receptor subtypes for treating certain disorders has not been determined nor has any use for ET-2, ET-3 been elucidated. The article, at page 1504, also teaches that the transition from peptidomimetic structures to a truly non-peptide lead compound, using "rational design", is a time-consuming and problematic endeavor.

Clozel et al, Nature, Vol. 365, 759-761 (1993). The Clozel reference discloses a structurally similar compound, RO 46-2005, (having an unsubstituted sulfoamide nitrogen) which has been extensively tested. However, the final paragraph teaches that those tests show only the potentia l of ET receptor antagonism as playing a role in the treatment of vasoconstriction, and that the validity of ET receptor antagonism in man remains to be determined.

Stein et al, Journal of Medicinal Chemistry, Vol. 37, No. 3, 329-331 (1994). The Stein article, published after the filing date, provides test data of ETA receptor antagonist, shown in Tables 1 and 2, of some structurally similar compounds (having an unsubstituted sulfoamide nitrogen) which are excluded by the instantly claimed proviso. In Table 2, the IC50 values differ over a 100-fold range just in changing substituents on the naphthyl ring. This evidences that small changes in structure will significantly affect the activity. The article also states, at page 329, right column, "proof that ET is a causative agent has remained elusive.....".

## Analysis:

There is demonstration in the specification that three compounds have been prepared. It is reasonable to conclude that the specification does teach how to make the entire scope of the claimed compounds. The issue is whether the specification teaches one skilled in the art at the time of filing how to use the invention as claimed. Based on the undue experimentation factors, particularly the state of the prior art, the unpredictability, the lack of working examples and guidance, and the breadth of the claims as evidenced by the information provided above, the answer would be no. Therefore, an objection/rejection using form paragraph 7.31.02 would be appropriate.

## The Rejection:

Claims 1-6 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Claim 1 recites compounds where the only disclosed uses of the compounds are the methods of treating various endothelin-related disorders as recited in claims 2-6. The specification discloses that the compounds act as endothelin receptor antagonists. However, the Doherty (page 1504), Stein (page 329), and Clozel (last paragraph) articles clearly establish that the field of effective ET receptor antagonists and their relation to treating known disease or ischemic conditions is uncertain. The references clearly evidence that at the time of filing there is no correlation between any one disorder and ET much less the laundry list of treatable diseases disclosed in the specification and claimed in claims 2-6. The references also provide evidence that the unpredictability in the art is extremely high. Note that Stein teaches that an unsubstituted sulfoamide nitrogen was critical to the receptor affinity of this class of ET receptor antagonists. Yet even for this narrow class of compounds there is a wide range of receptor binding , see Table 2. Additionally, receptor binding would be expected to be very much structure sensitive, see Stein article. Therefore, it is clear that at the time of filing there was no clear direction or guidance provided by the prior art to establish that the ET receptor antagonists disclosed (and claimed) are enabled in use for treatment of disease conditions such as hypertension, renal disorders, or ischemia.

Furthermore, the instant specification provides no direction or guidance for how to use the disclosed (and claimed) compounds since no protocol is set forth, and no working examples are provided. Although the specification provides a dosage range for treating conditions related to ET receptor antagonism there is no standard by which to measure whether the compounds will operate as intended. There are no guidelines for determination of dosages needed to provide an anti-hypertensive effect vs. anti-endotoxemia effect vs. anti-anginal effect, etc. Further, the instant claims embrace various non art-recognized equivalents of heterocyclics which can be substituted. The specific compounds made are not

seen as adequately representative of the compounds embraced by the extensive Markush groups instantly claimed. Therefore, one skilled in the art would not know how to use the invention as claimed throughout its entire scope without undue experimentation.

### Additional notes:

1. If the specification discloses compounds as antagonists for the ET receptor subtype ETA, which is selective for ET-1 (Doherty), and provides test data demonstrating that the three compounds prepared have the activity to inhibit ET-1 binding to vascular smooth muscle, then the specification would teach how to use those three compounds as ET-1 receptor antagonists. Claims drawn to those three compounds should not be rejected.
2. If the application is filed Jan. 1995, the specification clearly discloses compounds are antagonists for the ET receptor subtype ETA, and provides test data showing greater affinity for ET-1 over ET-3, then at least compounds tested can be used to treat hypertension. Douglas et al, TiPS, Vol. 15, 313-316 (1994), published before the filing date, teach that ET antagonists play a direct role for ET-1 in the maintenance of the elevated blood pressure. This demonstrates that the state of the prior art at the time of filing is a very important factor.

## Example I: Transgenic Animals

**Specification:** The specification discloses that -amyloid precursor protein (-APP) is associated in the art with Alzheimer's disease. At the time of filing, the art had only been able to diagnose Alzheimer's disease through the post mortem examination of the brains of patients who had exhibited the senile behavior characteristic of Alzheimer's. These examinations revealed the presence of neurofibrillary tangles formed from large plaques of agglomerated peptides. The brains show neuronal loss and abnormal morphology of the cells in the cortex and hippocampus. It was hypothesized in the art that when -APP is produced, it is cleaved in neuronal cells of the brain and its degradation product, /A4 protein, forms deposits which accumulate into plaques and then form tangles which eventually cause the death of brain cells. However, the specification admits that the sequelae of events leading to Alzheimer's disease is unknown.

The specification discloses that it would be beneficial to produce transgenic mice which could be used as a model for Alzheimer's disease so as to identify agents which can be used as therapeutic agents for Alzheimer's disease. The specification recognizes that mice normally produce their own -APP, but do not develop the symptoms of Alzheimer's disease. Thus, the specification is directed to the generation of mice which contain in their genome DNA encoding human /A4 protein. The specification discloses that the transgenic mice could be used to identify agents which inhibit the formation of the human /A4 protein. It is hypothesized that such agents would be useful therapeutics in treating Alzheimer's Disease since without the formation of the /A4 protein, there would be nothing to cause the changes associated with Alzheimer's disease.

Specific examples are provided which show the constructs used to make the mice. These constructs contain a glial-specific promoter and the coding sequence for /A4 protein. The transgenic mice are disclosed to express the /A4 protein, as verified by immunohistology. Some of the transgenic mice

additionally exhibit deposits of the /A4 protein in the brain. None of the mice are disclosed to possess amyloid plaques or neurofibrillary tangles. There is no disclosure that the animals were tested for behavioral effects.

## Claim:

1. A transgenic mouse, all of whose somatic and germ cells contain a construct which comprises a glial-specific promoter operatively linked to a DNA sequence which encodes human /A4 protein, said mouse expressing said construct in its glial cells.

## State of the Prior Art:

Selkoe, Nature, Vol. 354, 432-433 (1991).

This reference describes -APP and its relationship to Alzheimer's disease. The author states that -APP is a normal human protein, and that deposition of its cleavage product, /A4 protein, is a normal consequence of aging, and does not signify that a person will develop Alzheimer's disease. Furthermore, the reference states that although -APP and /A4 protein are associated with Alzheimer's disease, no correlation has been found between increased deposition of these proteins and the disease. In addition, the reference discloses that the mechanism by which the /A4 protein is formed and proceeds through the changes that lead to Alzheimer's Disease is unknown, but since the reference also discloses that the /A4 protein occurs in normal and Alzheimer's patients, the reference at least suggests that mechanisms are different in each type of patient.

## Analysis:

Since the **only** disclosed utility for the claimed mouse is a model for Alzheimer's disease so as to identify agents which can be used as therapeutic agents for Alzheimer's disease, enablement for the claimed invention must be based on whether the specification teaches how to make the claimed mouse and whether the specification teaches how to use the claimed mouse as a model for Alzheimer's disease so as to identify agents which can be used as therapeutic agents for Alzheimer's disease. The working examples in the specification show that transgenic mice have been generated which express human /A4 protein in their glial cells. Although some of the mice exhibit plaque formation, the reference of record indicates that deposition of /A4 protein does not necessarily indicate Alzheimer's disease is likely to develop. Furthermore, the reference discloses that the mechanism by which the /A4 protein is formed and proceeds through the changes that lead to Alzheimer's Disease is unknown, but since the reference also discloses that the /A4 protein occurs in normal and Alzheimer's patients, the reference at least suggests that mechanisms are different in each type of patient. Thus, it does not appear that the specification adequately teaches how the mice could be used as a model for Alzheimer's disease, or what conclusions could be drawn from the expression and deposition of human /A4 protein observed or the inhibition of human /A4 protein expression or deposition. Given the state of the art and the lack of guidance and working examples as to how to use the mice claimed, an enablement rejection using form paragraph 7.31.02 would be appropriate.

## Rejection:

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The claimed invention is directed to a transgenic mouse which expresses DNA encoding human /A4 protein in its glial cells. Applicant discloses that the mouse is useful for the identification of agents which inhibit human /A4 protein production, leading to therapies for Alzheimer's disease. However, the art teaches that in Alzheimer's disease, the patients suffer from neuronal loss and abnormal morphology of the cells in the hippocampus and cortex. The art does not indicate that glial cell production of human /A4 protein results in Alzheimer's Disease or any other disease. Selkoe, which represents the state of the art at the time the invention was made, does not make a correlation between an increase in human /A4 protein deposition and Alzheimer's disease. Indeed, the reference states that deposits of /A4 protein are found in human and other mammals that never develop Alzheimer's disease. As far as the disease is understood, the initial deposit of human /A4 protein must accumulate to form plaques which in turn lead to neurofibrillary tangles and neuronal death. Behavioral changes also occur such as inability to learn, short-term memory loss, etc. Furthermore, Selkoe discloses that the mechanism by which the /A4 protein is formed and proceeds through the changes that lead to Alzheimer's Disease is unknown, but since Selkoe also discloses that the human /A4 protein occurs in normal and Alzheimer's patients, Selkoe at least suggests that mechanisms are different in each type of patient. In view of these facts and the fact that applicant's mice do not exhibit plaque formation nor any morphological or behavioral indicia specific to Alzheimer's disease, inhibiting production of the human /A4 protein in the transgenic mice of the invention specification at best suggests that the formation of the protein could be inhibited in normal subjects but does not adequately disclose how to inhibit the formation of the protein in a patient with Alzheimer's Disease. Thus, given the unpredictability of the field of the invention, the relative lack of information available about Alzheimer's disease, and the lack of correlatability between the observed phenotype of the exemplified mice and any disease condition, others skilled in the art would be unable to practice the claimed invention without the exercise of undue experimentation.

**Modifications to the Above Facts:** Let us assume that the specification discloses that the transgenic mice produced actually exhibited at least one of the symptoms of Alzheimer's disease, e.g., the presence of neurofibrillary tangles, neuronal loss, and/or abnormal morphology of the cells like that exhibited in Alzheimer's disease, and the claim, in addition to the limitations recited above, recites that the transgenic mouse has the specifically disclosed phenotype. Does this change the analysis set forth above? The answer is yes. It would be reasonable to conclude that the disease mechanism of formation of the /A4 protein is being exhibited in the transgenic mice. Therefore, inhibiting the formation of the protein would be reasonably predictive of inhibiting the formation of the protein in a patient having Alzheimer's disease. Thus, in this case, no enablement rejection would be made.

In addition, no enablement rejection would be made in a situation where an enabled use for the claimed transgenic mouse is well established.

## Example J: Selectin-Mediated Cellular Adhesion

**Specification:** The specification discloses a series of compounds and compositions which are useful as inhibitors of P-selectin-mediated cellular adhesion. The compounds are disclosed as being effective in the treatment or prevention of inflammatory diseases such as rheumatoid arthritis, asthma and allergy conditions, as well as other pathological conditions including ulcerative colitis and multiple sclerosis.

The compounds of the invention have the following formula:


Chemical Structure 6

wherein R1, R2, R3, and R4 each are independently hydrogen, unsubstituted or substituted alkanoyl, arylalkyl or arylcarbonyl, wherein the substituent is selected from halogen, C1-4 alkyl, trifluoromethyl, hydroxy, and C1-4 alkoxy.

The specification provides detailed instruction for the synthesis of 30 inventive compounds. Furthermore, the specification provides 2 *in vitro* and 2 *in vivo* assays demonstrating the inhibitory effectiveness for 6 of the compounds on P-selectin-mediated cellular adhesion. The examples also demonstrate that three of the compounds failed to inhibit P-selectin-mediated cellular adhesion. General guidelines suggest that the compounds can be formulated in pharmaceutical compositions by combining them with pharmaceutical carriers. Several examples of suitable pharmaceutical carriers are given. The specification further discloses that the pharmaceutical compositions will contain suitable amounts of one of the compounds ranging from 0.1 µg/kg to 100mg/kg body weight, depending upon the type of formulation (systemic, topical, oral) and the particular disease or condition to be treated. Specific modes of administration are disclosed.

## Claims:

1. A compound of the formula:

1. 
Chemical Structure 6

   wherein R1, R2, R3, and R4 each are independently hydrogen, unsubstituted or substituted alkanoyl, arylalkyl or arylcarbonyl, wherein the substituent is selected from halogen, C1-4 alkyl, trifluoromethyl, hydroxy, and C1-4 alkoxy.

2. A pharmaceutical composition for treatment of diseases characterized by selectin-mediated cellular adhesion comprising a therapeutically effective amount of a compound of claim 1 with a pharmaceutically acceptable carrier.
3. A method for the treatment of diseases characterized by selectin-mediated cellular adhesion, comprising administering a therapeutically effective amount of a compound of claim 1 or a pharmaceutical composition thereof.

## State of the Prior Art:

WO 93/05803. This reference discloses that three human selectin proteins have thus far been identified, E-selectin (formerly ELAM-1), L-selectin (formerly LAM-1) and P-selectin (formerly PADGEM or GMP-140). This reference also discloses that inhibitors of selectin-mediated cellular adhesion are suitable as anti-inflammatory agents.

Skinner et al., J.Biol. Chem., Vol. 266, 5371-5374 (1991). This reference discloses that sulfated glycans inhibited the binding of P-selectin to neutrophils.

Suzuki et al., Biochem. Biophys. Res. Commun., Vol. 190, 426-434, (1993). This reference discloses that sulfated glycolipids are inhibitors of cellular adhesion.

Needham et al., Proc. Natl. Acad. Sci. USA, Vol. 90, 1359-1363, (1993). This reference discloses that sulfoglucuronyl glycosphingolipids (SGNL lipids) selectively support L- and P-selectin, but not E-selectin binding.

Mulligan et al., Nature, Vol. 364, 149-151, (1993). This reference discloses that oligosaccharides have useful protective effects in P-selectin-dependent lung injuries.

## Analysis:

The specification is sufficiently enabling to allow one skilled in the art to synthesize, without undue experimentation, the glycolipid compounds comprising the scope of claim 1 and the pharmaceutical composition comprising the scope of claim 2. Additionally, the specification does teach how to use 6 of the embodiments encompassed by claim 1 in the treatment of at least P-selectin-mediated cell adhesion disorders. Therefore, an enablement rejection using form paragraph 7.31.02 would not be appropriate. The question is whether the enabled embodiments are representative of the scope of the claims. There are two scope issues here. The first is regarding the scope of the compounds recited and the second is regarding the scope of selectin-mediated cellular adhesion. The art provides evidence that all the selectins are involved in mediating cellular adhesion. Furthermore, references such as Needham et al, Suzuki et al, and Skinner et al suggest that all the selectins are inhibited by similar compounds. Thus, the evidence given in the specification with respect to P-selectin would be expected to be applicable to at least one of the other selectins also. See Needham et al and Example 3 of WO 93/05803. It is true that it is not entirely predictable which compounds will inhibit binding of which selectin. The specification even provides evidence that some of the compounds meeting the structural limitations of the claims fail to inhibit P-selectin-mediated cellular adhesion. However, weighing all the evidence in this case, it would be reasonable to conclude that while the scope of the claims would encompass non-operative embodiments, the experimentation needed to determine the operative embodiments and to use those embodiments would not be undue. Therefore, it would be reasonable not to make any enablement or scope rejection in this case.

# Example K: HIV

**Specification:** The specification discloses Protein X, which is found on the surface of HIV having the amino acid sequence of SEQ ID NO. 1. The specification teaches the purification of Protein X from tissue culture supernatants containing HIV-infected cells and further teaches recombinant DNA methods for producing Protein X. An expression vector comprising a gene encoding Protein X was deposited with the ATCC prior to Applicant's filing date. The specification further discloses a composition containing Protein X and a carrier suitable for use in immunoassays for diagnosing HIV infection. The specification further discloses a pharmaceutical composition comprising Protein X suitable for treating and/or preventing HIV infection.

The specification also discloses a neutralizing monoclonal antibody designated Anti-X, specific for Protein X. The hybridoma producing Anti-X was deposited with the ATCC before Applicant's filing date as ATCC accession no. HB 12345. The specification discloses a composition comprising Anti-X suitable for use in decontaminating fluids containing HIV. The specification further discloses a pharmaceutical composition comprising Anti-X and a carrier suitable for passive immunization to treat and/or prevent HIV infection. The specification also discloses an immunoassay using Anti-X for diagnosing HIV infection.

The specification teaches methods of vaccination for the prevention of HIV infection by administering a pharmaceutical composition containing protein X. In support of the claimed invention, the specification teaches that Protein X injected into mice results in the production of antibodies which neutralize HIV *in vitro* as measured by viral inhibition assays and syncytium inhibition assays.

The specification further teaches a diagnostic assay method comprising contacting human serum with Protein X and then detecting the presence of human antibodies bound to Protein X. As evidence, the specification teaches the use of Protein X in a conventional ELISA assay using monoclonal antibody tissue culture supernatants. The specification further discloses that Protein X is useful for producing monoclonal antibodies suitable for decontaminating fluids containing HIV.

The specification further teaches a method for passive immunization against HIV by administering a pharmaceutical composition comprising Anti-X. Finally, the specification teaches a method of decontaminating a fluid containing HIV by contacting the fluid with Anti-X. The specification teaches that a concentration of 10 ng of Anti-X/ml of fluid will neutralize up to 109 HIV particles in both virus neutralization assays and syncytium inhibition assays thereby decontaminating the fluid.

The specification provides all the information and assurances so as to enable the making of all deposited materials. The specification also discloses specific dosages, administration techniques, and pharmaceutical carriers for each of the *in vivo* treatment methods.

## Claims:

1. Protein X having the amino acid sequence of SEQ ID NO. 1.
2. A composition comprising Protein X and a carrier.
3. A pharmaceutical composition suitable for treating HIV infection comprising the protein of claim 1 and a pharmaceutically acceptable carrier.
4. A vaccine for preventing HIV infection comprising the protein of claim 1.

5. A monoclonal antibody designated Mab X which specifically binds the protein of claim 1 and which is produced by the hybridoma having ATCC accession no. HB 12345.
6. A composition comprising the antibody of claim 5 and a carrier.
7. A pharmaceutical composition suitable for treating HIV infection comprising the antibody of claim 5 and a pharmaceutically acceptable carrier.
8. A vaccine for preventing HIV infection comprising the antibody of claim 5.
9. A method of treating a subject at risk for HIV infection comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of claims 2 or 7.
10. A method of preventing HIV infection in a subject comprising administering the vaccine of claim 3 in an amount sufficient to prevent HIV infection.
11. A method of passive immunization for preventing HIV infection comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 7.
12. A method for diagnosing HIV infection in a subject comprising:
13. **a) contacting a body sample with the protein of claim 1 for a time sufficient to allow antibodies in the body sample to bind to the protein;**
    **b) detecting the binding of said antibodies to said protein, wherein the binding of said antibodies is diagnostic of HIV infection.**

14. A method for diagnosing HIV infection in a subject comprising:
15. **a) immobilizing Anti-X on a solid support;**
    **b) contacting said immobilized Anti-X with a body sample for a time sufficient to allow binding of HIV virions in the sample to immobilized Anti-X;**
    **c) detecting the binding of HIV to said immobilized Anti-X, wherein the binding of HIV is diagnostic of HIV infection.**

16. An *in vitro* method for decontaminating a fluid containing HIV which comprises:
17. **a) contacting the fluid with the composition of claim 6 under conditions such that the composition forms a complex with the HIV;**
    **b) removing the complex so formed from the fluid, thereby decontaminating the fluid.**

## State of the Prior Art:

Well known in the art:

1. There are no known vaccines for preventing HIV infection;
2. There are no art-accepted animal models for HIV infection;
3. Antibodies have been used in HIV diagnostic assays and to remove substances and contaminants from fluids (affinity chromatography, autologous bone marrow transplant, etc.).

## Specific teachings of the art:

Fahey et al., Clin. exp. Immunol., Vol. 88, 1-5 (1992): No immune-based therapies for HIV have been shown to be effective; No clear correlations between various types of therapies and clinical benefits (see page 2, Table 1); Clinical benefits of antibody therapies is entirely unclear (see page 3, second column, third full paragraph).

Stein et al., CID, Vol. 17, 749-771 (1993): Intravenous immunoglobulins (IVIG) and passive immunization have not been effective (see pages 750-752). "Many of the approaches...such as the use of immunoglobulins and adoptive cell transfer, pose significant logistical problems in terms of expense and sources of donor material, while others (i.e., treatment with cytokines) are hampered by significant toxicity. Rational development of many approaches is limited by our current knowledge of their mechanisms and effects and of the immune system's complex and overlapping activities" (see page 765, last paragraph).

Fox, Bio/Technology, Vol. 12, (1994): "No therapy has emerged as a sure winner in the campaign against HIV, not a preventive vaccine nor any of the immune system-boosting treatments."

Seaver, Genetic Engineering News, pages 10 and 21 (1994): While monoclonal antibodies in general have found wide use in diagnostic assays, identification of a particular suitable antibody requires rigorous testing in the presence of serum proteins (see section entitled "Diagnostic Success Rates"). Identification of suitable therapeutic antibodies is even more difficult than finding suitable diagnostic antibodies (see section entitled "Therapeutic Mabs").

## Analysis:

The first question is whether Applicant has enabled one skilled in the art to make and use the claimed products. As with utility under 35 U.S.C. § 101, Applicant need only enable a single use to meet the requirements of 35 U.S.C. § 112, first paragraph. The major difference is that a single utility will obviate a rejection under 35 U.S.C. 101 for the entire claim. However, 35 U.S.C. 112, first paragraph, must have the single use enabled for the whole claim scope. Applicant has taught how to make Protein X as well as Anti-X (both with guidance and suitable deposits). Applicant has further shown that Protein X binds antibodies in assays. Since such assays for HIV are well known in the art, one skilled in the art would reasonably conclude that Protein X would function in a similar manner. Further, Applicant has enabled the use of Anti-X for decontaminating fluids since it was well known in the art to use antibodies to remove undesirable contaminants and Applicant's specification established that Anti-X was suitable for removing HIV from a fluid. Since Anti-X is enabled, Protein X, necessary for producing Anti-X, is also useful and, therefore, enabled by the specification. Thus, claims 1-2, 5-6, 12 and 14 would appear enabled.

For pharmaceutical compositions and vaccines, the intended use needs to be considered and given weight. A pharmaceutical composition has an implied *in vivo* use and evidence of enablement should be sufficient to convince one skilled in the art that the pharmaceutical composition would have some beneficial therapeutic effect. Likewise, the terminology "vaccine" by definition requires some form of protective immune response in an individual. With HIV, the art clearly recognizes that immune-based therapies have not been accepted by those skilled in the art. Therefore, one must carefully consider the evidence in the specification in support of *in vivo* uses. Here, the specification only teaches an *in vivo* response in mice to injections of Protein X. However, the mouse is not an art-accepted model for HIV. Neither are any *in vitro* assays accepted as correlative with *in vivo* efficacy. Therefore, claims 3-4 and 7-8 would not appear to be enabled by the specification.

Claims 9-11 are directed to various methods for treating or preventing HIV infection. However, Applicant's only evidence for treatment and/or prevention is in the mouse. The prior art does not recognize Applicant's animal model (or any other animal model) as correlating with efficacy in HIV infections. Nor has Applicant set forth any other evidence to establish that Protein X or Anti-X can be used to treat HIV or prevent HIV infections. Thus, the methods of claims 9-11 are not enabled.

Finally, claim 13 is directed to a diagnostic assay for diagnosing HIV infection using Anti-X. Diagnostic immunoassays using HIV proteins are well known. While Seaver teaches that monoclonal antibody-based assays are more difficult to develop than are protein assays, such as the Protein X assay of claim 12, this does not mean that such assays can not be developed or have not been developed. Furthermore, the specification indicates that Protein X is a surface protein and that the monoclonal antibodies described in the specification bind it with sufficient strength to actually neutralize the virus. Because of this strong binding to a surface protein, one of skill in the art would expect that the claimed method could be used at least to some extent for the diagnosis of HIV infection. Note, it is not necessary for an invention to work well to be enabled. Since neither Seaver nor the rest of the state of the art provide sufficient reason to doubt the objective enablement of the specification, claim 13 would appear enabled.

## Rejection:

Claims 3-4 and 7-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Applicant's claimed invention is directed to pharmaceutical compositions, vaccines and methods for diagnosing, treating and preventing HIV infection. However, the specification does not sufficiently establish that the pharmaceutical compositions, vaccines and methods can be used as claimed. The specification only sets forth evidence in the form of mouse animal model studies and there is insufficient evidence that such studies correlate with *in vivo* efficacy in HIV in humans. It is well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies, as taught by Fahey et al. The obstacles to therapy of HIV are well documented in the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed pharmaceutical compositions and vaccines to treat and/or prevent HIV infection without undue experimentation.

Further, it is well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Further, as taught by Fahey et al., clinical trials using a variety of immunologically based therapies have not yielded successful results in the treatment and/or prevention of HIV infection. Fahey et

al. particularly discloses that monoclonal antibody therapies have not provided any clinical benefits and "it is not clear how adding these additional antibodies would make a difference" (see page 3, second column, third full paragraph). This is further evidenced by the teachings of Stein et al. which states that rational development of HIV therapeutics "is limited by our current knowledge of their mechanisms and effects and of the immune system's complex and overlapping activities" (see page 765, last paragraph). The failure of all immune-system-boosting therapies for treating AIDS is further discussed by Fox (see last paragraph). Thus, it is clear from the evidence of Fahey et al., Stein et al. and Fox, that the ability to treat and/or prevent HIV infection is highly unpredictable and has met with very little success. Applicants have not provided any convincing evidence that their claimed invention is indeed useful as a therapeutic or preventative for HIV infection and have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

# Example L: Alzheimer's Disease

**Specification:**The specification discloses compounds of formula


Chemical Structure 7

wherein A is a linking group and Ar is phenyl or piperazinyl, or pharmaceutically acceptable salts thereof. The specification describes five different linking groups and provides test data with each compound showing that they specifically bind to muscarinic receptors. The specification discloses methods for synthesizing the compounds. The compounds are disclosed for the treatment of Alzheimer's disease, particularly the cognitive impairment aspect of the disease, and general dosages, administrations, and pharmaceutical carriers are described but the specification has no working examples to demonstrate that the compounds affect the function of the muscarinic receptor or treat Alzheimer's disease.

## Claims:

1. A compound of formula

1. 
Chemical

   wherein A is a linking group and Ar is phenyl or piperazinyl, or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition useful for treating Alzheimer's disease comprising a pharmaceutically acceptable carrier and a therapeutically-effective amount of a compound as claimed in claim 1.
3. A method of treating Alzheimer's disease in a mammal in need of such treatment, which comprises administering to said mammal a therapeutically-effective amount of a compound as claimed in claim 1.

## State of the prior art:

Patel, Journal of Geriatric Psychiatry and Neurology, Vol. 8, 81-95, (1995) - This reference discloses that Alzheimer's disease is known to be difficult to treat and that there is neither a clear understanding of the origin and pathophysiology of AD (Alzheimer's disease) nor an animal model of the illness. See Patel, page 81. The reference states that the search for an effective cognition-enhancing therapy for AD has so far proved to be elusive. See Patel, page 90.

Ehlert et al, Life Sciences, Vol. 55, Nos. 25/26, 2135-2145, (1994) - This reference teaches that 5 different subtypes (M1-M5) of muscarinic receptors have been discovered, and that the activities and species variation in distribution are complicated. M2 and M4 are taught to have selective coupling to inhibition of adenylate cyclase, while M1-M3-M5 couple to a different hydrolysis, see pages 2137-8. The reference also provides detailed discussion regarding treatment of AD with a directly acting muscarinic agonist or an allosteric muscarinic agonist but specifically states at page 2142 that "no allosteric agonists for the muscarinic receptor have been described so far."

## Analysis:

There is a description in the specification as to how to synthesize the claimed compounds. Therefore, the specification clearly teaches how to make the claimed compounds. Accordingly the question is whether the specification teaches how to use the claimed compounds.

For claim 1, there is only one explicitly disclosed method for using the claimed compounds, i.e., the claimed method for treating Alzheimer's disease. However, since the specification teaches that the claimed compounds specifically bind to the muscarinic receptor and Ehlert et al teach that muscarinic receptors can be detected by their binding characteristics, it would be reasonable to conclude that the claimed compounds would have a well established use of detecting the muscarinic receptor and that one of skill in the art would know how to use the compounds for detecting muscarinic receptor without undue experimentation. Accordingly, it would be inappropriate to include claim 1 in a rejection under 35 U.S.C. 112, first paragraph.

With respect to claim 2, the "pharmaceutical", "pharmaceutically acceptable", and "therapeutically-effective" language in combination with the fact that the only disclosed pharmaceutical use of the compositions is for treating Alzheimer's disease leads to the conclusion that this claim should be evaluated in terms of whether the specification teaches how to use the compositions for treating Alzheimer's disease. Since method claim 3 must be evaluated in terms of the recited use, treating Alzheimer's disease, claims 2-3 should be evaluated together. In this case, the state of the art teaches the unpredictability in treating Alzheimer's disease, that there are no acceptable models for treating Alzheimer's disease, and that there are no know agonists of the muscarinic receptors known that are sufficient to treat Alzheimer's disease. Furthermore, while the specification clearly discloses that the claimed compounds bind to the muscarinic receptors, there is no indication that the binding effects or activates the receptor in any way. Binding does not equal activating. This, coupled with the state of the art teaching that there are no models, leads to the conclusion that there are no working examples. Therefore, based on the undue experimentation factors, particularly the unpredictability, the lack of further guidance,

and the lack of working examples (as evidenced by the information provided by the state of the prior art), it would be reasonable to conclude that it would require undue experimentation to use the invention of claims 2-3 and a rejection using form paragraph 7.31.02 would be appropriate.

## Rejection:

Claims 2-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The claims recite compositions for treating Alzheimer's disease (AD) and methods of using compounds for treating Alzheimer's disease. AD is arguably the most intractable of all major medical disorders. Specifically, Patel states at page 81:

To date, there is neither a clear understanding of the origin and pathophysiology of AD nor an animal model of the illness.

This is also evidence of the extreme difficulty and unpredictability in treatment of AD. A wide variety of therapeutic strategies for treating AD is being pursued. The major categories of these strategies are collected in Table 1 of Patel (page 82). Relevant here is the Cholinergic Drugs subcategory, and in particular, the subsubcategory "Receptor Agonists" (see page 84). It can be seen that muscarinic agonists is just one of many, many strategies being pursued. Patel notes the unpredictability of using muscarinic agonists to improve cognition in AD patients.

As Ehlert notes, 5 different subtypes (M1-M5) of muscarinic receptors have been discovered, and that the activities and species variation in distribution are complicated. M2 and M4 are taught to have selective coupling to inhibition of adenylate cyclase, while M1-M3-M5 couple to a different hydrolysis, see pages 2137-8. Ehlert, page 2142, suggests that the presence of an allosteric site on the receptor may actually be the route to an effectiveness not previously shown. He also observes states:

Although no allosteric agonists for the muscarinic receptor have been described so far, it is possible that structural modification of the gallamine molecule could lead to the identification of a drug that increases the affinity of acetylcholine.

The specification provides data to show that the instant compounds bind to the muscarinic receptors, but the fact that the compounds bind to the receptors does not mean that they are muscarinic agonists. Binding does not equal activation. Accordingly, the specification fails to provide any working examples. Further, the most recent research has emphasized the necessity of selectivity. Applicants have not demonstrated any of this. In addition, there is no teaching how the data provided permits the determination of an effective amount for treating AD. Therefore, in view of the unpredictability in the art, the lack of working examples, and the lack of further guidance in how to use the claimed compounds and compositions to actually treat AD, it would require an undue amount of experimentation to use the claimed inventions.

# Example M: Polymers

**Specification:** The specification discloses methods of making polymeric articles comprising polyolefins. The specification states that when the polyolefins are mixed with diphosphites prior to normal processing into articles, such as by blow molding or extrusion at temperatures of about 600oC, the presence of the diphosphite stabilizes the polyolefin containing article against discoloration. Polyolefins suitable for utilization in the invention are disclosed as including homopolymers and copolymers of mono-olefins, such as polyethylene and polypropylene and copolymers of ethylene and propylene. Crosslinked polyolefins are also disclosed as being suitable for purposes of the invention. The disclosed crosslinked polyolefins which are suitable for the invention are those which have been formulated utilizing conventional peroxide crosslinking agents for polyolefins, such as dicumyl peroxide and di-t-butyl peroxide.

The specification discloses that the diphosphites suitable for use in the invention include bis-(alkylphenyl) pentaerythritol diphosphites such as bis-(2,4-ditertiarybutylphenyl)pentaerythritol diphosphite. Several other specific diphosphites are disclosed as are several different forms for the diphosphites, such as dry powder or dissolved in a solvent. The specification discloses that when the diphosphites are employed in the polymeric composition at certain concentrations, they are effective in stabilizing the polyolefin during thermal processing conditions against discoloration. The diphosphites are admixed with the polyolefin prior to processing and at a concentration of about 0.01 to about 5.0% by weight of the stabilized composition depending on the particular polyolefin and processing conditions. The specification explicitly states: "This concentration range is critical for stabilization against discoloration of the polyolefins because discoloration readily occurs when the diphosphites are used at concentrations below or above this concentration range." The diphosphite stabilizers are preferably employed within a range of 0.05 to about 2.0%. and most preferably within a range of 0.1 to about 1.0%.

## Claims:

1. A method of making a polyolefin containing article stabilized against discoloration comprising forming a composition comprising a polyolefin and a diphosphite and then processing the composition to form the article.
2. The method of claim 1 wherein the composition includes 0.01 to 5% by weight of the diphosphite **.**
3. The method of claim 2 wherein the composition includes 0.05 to 2% by weight of the diphosphite.
4. The method of claim 2 wherein the composition includes 0.1 to 1% by weight of the diphosphite.

**State of the Prior Art:** It is well known in the art that diphosphites decompose and, therefore, lose their activity when exposed to temperatures in excess of 1000oC.

Blow molding and extruding using polyolefins are well known processes for producing polymeric articles and are carried out at temperatures ranging from 250oC to 1500oC.

## Analysis:

In this case, there are no working examples given in the specification. However, the lack of any working examples alone cannot serve as the only reason for making an enablement rejection. The other undue experimentation factors must also be considered. Here, the art of making polyolefin containing articles by processes such as blow molding and extrusion are well known and relatively predictable, the specification provides ample guidance with respect to polyolefins and diphosphites suitable for carrying out the invention, and the claims are limited to producing polyolefin containing articles. Thus, the other undue experimentation factors appear to point toward the claimed invention being enabled. The only possible issues regarding lack of enablement appear to be those dealing with the temperature of the processing and the concentration of the diphosphite.

Regarding the temperature, the claim is not limited to any particular processing temperature but it is clear from the state of the art that the process would not be operative at temperatures above 1000oC since the diphosphites decompose and become inactive. Since the specification explicitly discloses processes being carried out about 600oC, it appears that the claims should be limited to processes being carried out at about 600oC. However, there is nothing in the specification which indicates that the temperature of the process is critical to produce polyolefin containing articles stabilized against discoloration. Furthermore, the specification need not disclose what is well known in the art, and preferably omits it, and the claims can include non-operative embodiments as long as is does not require undue experimentation to determine which embodiments are operable. Here, one skilled in the art taking the specification with the state of the art, would clearly recognize the temperature limitations of the claimed processes and would be able to determine which embodiments are operable without undue experimentation. Therefore, it would be improper to limit the claims to a particular temperature.

Regarding the concentration issue, the specification explicitly states that when the concentration of the diphosphites in the composition is outside the range of 0.01 to 5% by weight, the articles are not stabilized against discoloration and, therefore, the concentration is critical to the invention. Since claim 1 lacks this critical limitation, it would be reasonable to reject claim 1 for lack of enablement using form paragraph 7.33.01. Since claims 2-4 include concentrations within the critical range, they would not be included in the rejection. Note, while the specification also states that narrower concentration ranges are "preferred", this does not mean that they are critical. Therefore, it would be inappropriate to limit the claims to these narrower concentrations.

## Rejection:

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The concentration of the diphosphite in the composition is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. *In re Mayhew* , 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The specification clearly discloses that the concentration of the diphosphite is critical to the making of polyolefin containing articles that are stabilized against discoloration when it states:

This concentration range is critical for stabilization against discoloration of the polyolefins because discoloration readily occurs when the diphosphites are used at concentrations below or above this concentration range.

Therefore, the claim should be limited to such concentrations.

# Example N: DNA

**Specification:** The 50 amino acid peptide, algernin, has been extracted and isolated from ovine brain. Algernin has been sequenced and cDNA clones encoding algernin have been isolated from both sheep and humans. The human cDNA is similar to the ovine cDNA and encodes the same amino acid sequence as the ovine cDNA. The specification also discloses probes consisting of 15 or more consecutive nucleotides from the cDNA sequences encoding ovine or human algernin and that the probes can be used to isolate the corresponding cDNA. Specific procedures and working examples are described for using the probes to isolate the algernin gene as are specific constructs, procedures and working examples for the recombinant production of active algernin in prokaryotic and eukaryotic cells. Preliminary test results with human subjects show that injections of purified algernin (0.005 mg/kg) increases short term memory retention by 200% compared to injections of human serum albumin. Algernin also significantly decreases the time required for mice to learn to run simple mazes.

TABLE 1 (amino acid sequence of algernin)

Met Phe Arg Val Lys Arg Trp Thr Phe Val Leu Val Val Lys Thr Val Gln Met

Ala Lys Phe Gln Trp Met Ala Lys Ile Phe Trp Val Trp Thr Val Cys Val Arg

Thr Val Glu Phe Arg Val Lys Arg Val Val Met Ala Met Lys

TABLE 2 (ovine cDNA for algernin)

ATG TTT CGA GTC AAG AGG TGG ACC TTC GTA TTG GTC GTA AAG ACT GTG GAG ATG

Met Phe Arg Val Lys Arg Trp Thr Phe Val Leu Val Val Lys Thr Val Gln Met

GCC AAA TTT GAA TGG ATG GCG AAA ATA TTT TGG GTA TGG ACC GTG TTC GTA CGG

Ala Lys Phe Gln Trp Met Ala Lys Ile Phe Trp Val Trp Thr Val Cys Val Arg

ACA GTT GAA TTT CGG GTG AAA CGG GTA GTA ATG GCC ATG AAA TAG

Thr Val Glu Phe Arg Val Lys Arg Val Val Met Ala Met Lys

TABLE 3 (human cDNA for algernin)

ATG TTC CGA GTC AAG AGA TGG ACC TTC GTA TTA GTC GTA AAG ACT GTG GAG ATG

Met Phe Arg Val Lys Arg Trp Thr Phe Val Leu Val Val Lys Thr Val Gln Met

GCC AAA TTT GAA TGG ATG GCG AAA ATA TTT TGG GTA TGG ACC GTG TTC GTA CGG

Ala Lys Phe Gln Trp Met Ala Lys Ile Phe Trp Val Trp Thr Val Cys Val Arg

ACA GTT GAA TTT CGG GTG AAA CGG GTA GTA ATG GCC ATG AAG TAG

Thr Val Glu Phe Arg Val Lys Arg Val Val Met Ala Met Lys

## Claims:

1. An isolated cDNA that comprises the following DNA sequence and encodes algernin:

1. ATG TTC CGA GTC AAG AGA TGG ACC TTC GTA TTA GTC GTA AAG ACT

   GTG GAG ATG GCC AAA TTT GAA TGG ATG GCG AAA ATA TTT TGG GTA

   TGG ACC GTG TTC GTA CGG ACA GTT GAA TTT CGG GTG AAA CGG GTA

   GTA ATG GCC ATG AAG TAG

   or fragments thereof that are at least 15 nucleotides in length.

2. An isolated DNA that encodes the following amino acid sequence for algernin:
3. Met Phe Arg Val Lys Arg Trp Thr Phe Val Leu Val Val Lys Thr Val Gln Met Ala Lys Phe Gln Trp Met Ala Lys Ile Phe Trp Val Trp Thr Val Cys Val Arg Thr Val Glu Phe Arg Val Lys Arg Val Val Met Ala Met Lys

   or fragments thereof that are at least 15 nucleotides in length.

4. An isolated DNA that encodes a 50 amino acid peptide that has algernin activity.

## State of the Prior Art:

Ngo et al, The Protein Folding Problem and Tertiary Structure Prediction , 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495. This reference teaches that the relationship between the sequence of a peptide and its tertiary structure (i.e., its activity) is not well understood and is not predictable.

The state of the prior art is also such that given a specific sequence it is routine to synthesize DNA and proteins.

## Analysis:

Claim 1 is limited to a single DNA sequence and any 15 mer thereof. Since the state of the art is such that it would have been routine to make the DNA given the sequence, it certainly would not require undue experimentation to make the DNAs claimed in claim 1. Furthermore, the specification clearly shows how to use the full length DNA to produce algernin and the 15 mers to obtain the full length DNA. Therefore, it would not require undue experimentation to make or use the DNAs of claim 1 and no enablement rejection should be made.

For claim 2, the analysis is similar even thought the genus is very large. There are at least 1.26 x 1021 embodiments of the claim, but each embodiment can be readily identified using the genetic code, synthesized using conventional methods, and used in the manner taught in the specification without undue experimentation.

For claim 3 the analysis is different. Claim 3 is broader than the enabling disclosure because there is no guidance as to which (if any) of the 50 amino acids may be changed while algernin activity is retained. The total number of 50 amino acid peptides is 1.13 X 1065. The number of single amino acid substitutions is 950. The number of two amino acid substitutions is over 900,000. Since the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction , 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.), it would require undue experimentation for one skilled in the art to arrive at other 50 amino acid peptides that have algernin activity. In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* , 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other genetic sequences that are embraced by the claim. If it would require undue experimentation to identify other 50 amino acid peptides that have algernin activity, it certainly would require undue experimentation to make their corresponding DNA. Therefore, it would be reasonable to conclude that it would require undue experimentation to make the entire scope of claim 3. Since there are embodiment within the scope of claim 3 that are enabled, such as those recited in claims 1 and 2, the rejection should be made using form paragraph 7.31.03.

## Rejection:

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA encoding the amino acid sequence for algernin, does not reasonably provide enablement for DNA that encodes other 50 amino acid peptides that have algernin activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 3 recites DNA that encodes any 50 amino acid peptide as long as the peptide has algernin activity. However, other than algernin itself, the specification fails to disclose any other peptide which has algernin activity. Furthermore, the specification provides no guidance as to which (if any) of the 50 amino acids may be changed while algernin activity is retained. The total number of 50 amino acid peptides is 1.13 X 1065. The number of single amino acid substitutions is 950. The number of two amino acid substitutions is over 900,000. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain algernin activity, and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction , 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.), it would

require undue experimentation for one skilled in the art to arrive at other 50 amino acid peptides that have algernin activity. In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* , 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other genetic sequences that are embraced by the claim. This is the case here. In other words, since it would require undue experimentation to identify other 50 amino acid peptides that have algernin activity, it certainly would require undue experimentation to make their corresponding DNA and, therefore, the entire scope of claim 3 is not enabled.

**Modifications to the Above Facts:** Let us assume that the specification merely disclosed that the algernin could be used to increase short term memory retention but does not teach how to use algernin in this or in any other manner and there is no well established use for algernin. Also assume that the application includes a claim directed to a method of making algernin using cDNA encoding algernin and there is no well established use for the claimed cDNA. Thus, in this situation, the only disclosed use for the claimed inventions is making algernin, which the specification teaches how to do, but the specification fails to teach how to use algernin. Does this change the analysis set forth above? Put another way, does the specification need to teach how to use a product before claims directed to a method of making the product and claims directed to materials to be used in making the product are considered enabled? The answer to this last question is yes. Under these circumstances, a claim drawn to a method of making the product and claims drawn to materials used in the method of making the product are not enabled and an appropriate enablement rejection can be made.

# Example O: Vaccines

**Specification:** The specification relates to *Lysobacteria erythrosis* , the microorganism which causes erythrosis, a slow acting yet deadly disease manifested by the lysis of the erythrocyte in patients infected with the microorganism. The disclosure states that *l. erythrosis* has many proteins on the surface thereof and that one of these proteins in particular can induce the immune system to produce antibodies. The specific surface protein disclosed includes the following peptide which is responsible for the production of the antibodies:

1 5 10 15

Ser Thr Ile Phe Leu Glu Ser Thr His Glu Asp Ile Ser Glu Ala Ser Glu

The specification describes compositions including the peptide and a carrier and teaches that the composition can be used to induce the immune system, e.g., to produce antibodies which will serve to vaccinate the host against erythrosis without causing the disease itself. Specific pharmaceutically acceptable carriers are described as are specific concentrations of the peptide in the compositions and suitable modes of administration for generating the immune response. The specification states that the

peptide can be made using routine peptide synthesis techniques. The specification includes one example which synthesizes the peptide, places the peptide in a carrier to form a composition, injects the composition into a rabbit three times over a period of two months. Three days after the last injection, the rabbit was bled and antibodies against *l. erythrosis* were isolated. The antibodies were contacted with blood samples from normal patients and those diagnosed with erythrosis. Binding was present in the samples from the patients with erythrosis but no binding was present in the samples from normal patients. It was not demonstrated whether the antibodies were protective against the disease.

## Claims:

1. A peptide have the following amino acid sequence:

1. Ser Thr Ile Phe Leu Glu Ser Thr His Glu Asp Ile Ser Glu Ala Ser Glu.

2. 2. A vaccine comprising the peptide of claim 1 and a pharmaceutically acceptable carrier.
3. 3. A method of inducing an immune response in a host comprising administering to the host a composition comprising the peptide of claim 1 and a carrier.

**State of the Prior Art:** Diagnostic assays for erythrosis are known in the art. Those assays typically utilize antibodies against surface antigens of *l. erythrosis* , contact the antibodies with blood samples from a patient, and check for any antibody binding, wherein any binding is indicative of the presence of the microorganism.

Nathaniel et al (this is a fictitious reference) - This reference teaches that no vaccines for erythrosis are known. While there have been many attempts at producing a vaccine, all have resulted in failure. Erythrosis is known only to affect humans. While the microorganism will infect other mammals, no other mammal other than humans get the disease. No animal models are recognized as being predictive of vaccination in humans.

## Analysis:

For claim 1, the specification discloses how to make the claimed peptide. Furthermore, while the only explicitly disclosed use for the peptide is as a vaccine, which may not be enabled, the example taken with the state of the prior art implies a well established utility of using the peptide to raise antibodies for using in assays for erythrosis. Since one would know how to use the peptides and the resultant antibodies from the specification and the state of the art without undue experimentation, it would be inappropriate to reject claim 1 for lack of enablement.

With respect to claim 2, the "vaccine" and "pharmaceutically acceptable carrier" language in combination with the fact that the only disclosed pharmaceutical use of the compositions is for a vaccine leads to the conclusion that this claim should be evaluated in terms of whether the specification teaches how to make and use the composition as a vaccine. While the specification provides some guidance regarding vaccination, it would be reasonable to conclude that it would require an undue amount of experimentation to use the composition as a vaccine in view of the unpredictability in the art and the lack

of working examples. For the reasons set forth above with respect to claim 1, it is clear that non-vaccine compositions would be enabled. Since some compositions are enabled, it would be best to make a scope rejection using form paragraph 7.31.03.

Claim 3 is a broad claim. When read in light of the specification and the state of the prior art, it covers methods of producing antibodies for use in diagnostic assays as well as vaccination. Thus, claim 3 must be evaluated as to whether the specification enables the entire scope of the claim. From the above discussion with respect to claims 1 and 2, it is clear that the specification enables the method to the degree that it encompasses producing antibodies, but not to the degree that it encompasses vaccination. Therefore, it would be reasonable to make a scope rejection using form paragraph 7.31.03.

## Rejection:

Claims 2-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabled for non-vaccine compositions and non-vaccination methods of inducing an immune response, does not reasonably provide enablement for vaccine compositions and their use in vaccination against erythrosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 2 is directed to a vaccine, the only disclosed use being vaccination against erythrosis. Claim 3 is directed to a method which encompasses the use of the peptide for vaccination against erythrosis. However, the specification fails to adequately teach how to use the composition and method for vaccinating against erythrosis. Erythrosis is a deadly disease and many attempts at producing a vaccine have been made with no success. This is evidenced by Nathaniel et al. Thus, the art of vaccinating against erythrosis is not predictable. While the specification does provide some general guidance with respect to how to use the vaccine, there are no working examples since the induction of antibodies in rabbits does not necessarily mean that the antibodies are protective, since humans are the only ones afflicted with the disease, and since the rabbits do not constitute a recognized animal model as is apparent from the state of the prior art. In view of the absence of working examples for vaccinating against erythrosis, the breadth of the claims, and the unpredictable state of the art with respect to vaccinating against erythrosis, it would require undue experimentation for one skilled in the art to practice the entire scope of the claimed invention.

If claims 2 and 3 were limited as follows, this rejection would be overcome:

**2. A composition comprising the peptide of claim 1 and a carrier.**
**3. A method of producing antibodies which recognize *lysobacteria erythrosis* in a host comprising administering to the host a composition comprising the peptide of claim 1 and a carrier.**

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Sambrook et al, Molecular Cloning, A Laboratory Manual , Second Edition, 1989, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, p. 11.47.

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## EXAMPLE D:

NONE

## EXAMPLE E:

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## EXAMPLE M:

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## EXAMPLE N:

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## EXAMPLE O:

NONE

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