Chapter 2400 Biotechnology

2401 Introduction

This chapter provides guidance on the practices and procedures for implementation of the deposit rules (37 CFR 1.801 – 1.809) and the sequence rules (37 CFR 1.821 – 1.825). The final rule for deposits of biological materials for patent purposes was published in the *Federal Register*, 54 FR 34864 (August 22, 1989) and in the *Official Gazette*, 1106 O.G. 37 (September 12, 1989). The deposit rules went into effect on January 1, 1990. The final rule for the requirements for patent applica-

tions containing nucleotide sequence and/or amino acid sequence disclosures was published in the *Federal Register*, 55 FR 18230 (May 1, 1990) and in the *Official Gazette*, 1114 O.G. 29 (May 15, 1990) and went into effect on October 1, 1990. Revised sequence rules were published in the *Federal Register* at 63 FR 29620 (June 1, 1998) and in the *Official Gazette* at 1121 O.G. 82 (June 23, 1998) and went into effect on July 1, 1998.

Additional information regarding the development of the deposit rules can be obtained in the text of the draft policy statement, published in BNA's *Patent, Trademark and Copyright Journal*, 32 PTCJ 781 at 76, 90 (May 22, 1986), the advanced notice of proposed rulemaking, published in the *Federal Register*, 52 FR 34080 (September 9, 1987), and in the *Official Gazette*, 1082 O.G. 47 (September 29, 1987) and in the notice of proposed rulemaking, published in the *Federal Register*, 53 FR 39420 (October 6, 1988), and in the *Official Gazette*, 1095 O.G. 47 (October 25, 1988). Additional information regarding the development of the sequence rules can be obtained in the text of the notice of proposed rulemaking, published in the *Federal Register*, 54 FR 18671 (May 2, 1989) and in the *Official Gazette*, 1102 O.G. 34 (May 16, 1989).

See MPEP § 803.04 and § 1850 for restriction and unity of invention practice respectively in patent applications claiming independent and distinct nucleotide sequences. See also MPEP § 2434.

2402 The Deposit Rules

Every patent must contain a written description of the invention sufficient to enable a person skilled in the art to which the invention pertains to make and use the invention. Where the invention involves a biological material and words alone cannot sufficiently describe how to make and use the invention in a reproducible manner, access to the biological material may be necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112. Courts have recognized the necessity and desirability of permitting an applicant for a patent to supplement the written disclosure in an application with a deposit of biological material which is essential to meet some requirement of the statute with respect to the claimed invention. *Merck and Co., Inc. v. Chase Chemical Co.*, 273 F. Supp. 68, 155 USPQ 139 (D. N.J. 1967); *In re Argoudelis*, 434 F.2d 666, 168 USPQ 99 (CCPA 1970). To facilitate the recognition of deposited biological material in patent applications throughout the world, the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure was established in 1977, and became operational in 1981. The Treaty requires signatory countries, like the United States, to recognize a deposit with any depository which has been approved by the World Intellectual Property Organization (WIPO).

The deposit rules (37 CFR 1.801 – 1.809) set forth examining procedures and conditions of deposit which must be satisfied in the event a deposit is required. The rules do not address the substantive issue of whether a deposit is required under any particular set of facts.

The rules are effective for all applications filed on or after January 1, 1990, and for all reexamination proceedings in which the request for reexamination was filed on or after January 1, 1990, except that deposits made prior to the effective date which were acceptable under the then current practice will be acceptable in such applications and proceedings. Since most of the provisions of the rules reflect policy and practice existing prior to January 1, 1990, little change in practice or burden on applicants for patent and patent owners relying on the deposit of biological material has occurred. Applicants and patent owners are encouraged to comply with these rules even if their applications and reexamination proceedings were filed prior to January 1, 1990.

2403 Deposit of Biological Material

37 CFR 1.801. Biological material.

For the purposes of these regulations pertaining to the deposit of biological material for purposes of patents for inventions under 35 U.S.C. 101, the term biological material shall include material that is capable of self-replication either directly or indirectly. Representative examples include bacteria, fungi including yeast, algae, protozoa, eukaryotic cells, cell lines, hybridomas, plasmids, viruses, plant tissue cells, lichens and seeds. Viruses, vectors, cell organelles and other non-living material existing in and reproducible from a living cell may be deposited by deposit of the host cell capable of reproducing the non-living material.

37 CFR 1.801 indicates that the rules pertaining to deposits for purposes of patents for inventions under 35 U.S.C. 101 are intended to relate to biological material. For the purposes of these rules, the term "biological material" is defined in terms of a non-exhaustive list of representative materials which can be deposited in accordance with the procedures defined in these rules. These rules are intended to address procedural matters in the deposit of biological material for patent purposes. They are not designed to decide substantive issues such

as whether a deposit of a particular organism or material would be recognized or necessary for the purposes of satisfying the statutory requirements for patentability under 35 U.S.C. 112. Although the issue of the need to make a deposit of biological material typically arises under the enablement requirement of the first paragraph of 35 U.S.C. 112, the issue could also arise under the description requirement (35 U.S.C. 112, first paragraph), best mode requirement (35 U.S.C. 112, first paragraph) or the requirements of the second paragraph of 35 U.S.C. 112 with respect to the claims.

37 CFR 1.801 does not attempt to identify what biological material either needs to be or may be deposited to comply with the requirements of 35 U.S.C. 112. For the most part, this issue must be addressed on a case–by–case basis. Thus, while the Office does not currently contemplate that there would be any situations where a material that is not capable of self–replication either directly or indirectly would be acceptable as a deposit, an applicant is clearly not precluded by these rules from attempting to show in any given application why the deposit of such a material should be acceptable to satisfy the requirements of 35 U.S.C. 112.

2403.01 Material Capable of Self–Replication

Biological material includes material that is capable of self–replication either directly or indirectly. Direct self–replication includes those situations where the biological material reproduces by itself. Representative examples of materials capable of self–replication are defined in the rule. Indirect self–replication is meant to include those situations where the biological material is only capable of replication when another self–replicating biological material is present. Self–replication after insertion in a host is one example of indirect self–replication. Examples of indirect replicating biological materials include viruses, phages, plasmids, symbionts, and replication defective cells. The list of representative examples of each type of replicating material includes viruses to demonstrate that the two lists in the rule are not intended to be mutually exclusive.

2403.02 Plant Material

Although plant material is included within the scope of the definition of biological material for purposes of patents for plant inventions under 35 U.S.C. 101, the rules on deposits are not applicable to applications filed under the Plant Patent Act (35 U.S.C. 161–164). The Office is of the view that a deposit is not required under the present provisions of 35 U.S.C. 162. Thus, a deposit is not necessary for the grant of a plant patent under the provisions of 35 U.S.C. 161–164. As with other biological material deposited for purposes of patents for inventions under 35 U.S.C. 101, the deposit of plant material together with the written specification must enable those skilled in the art to make and use the claimed invention, in accordance with the requirements of 35 U.S.C. 112.

As with some types of reproducible biological material, seeds can be reproduced only after a growing season which may be relatively long. Although the rules do not specify a specific number of seeds to be deposited to meet the requirements of these rules, the Office will consider 2500 to be a minimum number in the normal case, but will give an applicant the opportunity to provide justification why a lesser number would be suitable under the circumstances of a particular case. The Department of Agriculture requires a deposit of 2500 seeds for the grant of a Plant Variety Protection Certificate under the Plant Variety Protection Act (7 U.S.C. 2321 *et seq.*). As the reproduction of seeds will often take a substantial period of time, the Office will require, at a minimum for the grant of a patent, a number of seeds that is likely to satisfy demand for samples once the patent is granted. In one instance, the Office accepted a deposit of 600 seeds coupled with an undertaking to deposit 1900 more seeds with due diligence. The particular situation involved a "seedless" vegetable with very few seeds per "fruit;" about two growing seasons were required to provide the additional 1900 seeds.

2404 Need or Opportunity to Make a Deposit

37 CFR 1.802. Need or opportunity to make a deposit.

(a) Where an invention is, or relies on, a biological material, the disclosure may include reference to a deposit of such biological material.

(b) Biological material need not be deposited unless access to such material is necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112. If a deposit is necessary, it shall be acceptable if made in accordance with these regulations. Biological material need not be deposited, inter alia, if it is known and readily available to the public or can be made or isolated without undue experimentation. Once deposited in a depository complying with these regulations, a biological material will be considered to be readily available even though some requirement of law or regulation of the United States or of the country in which the depository institution is located permits access to the material only under conditions imposed for safety, public health or similar reasons.

(c) The reference to a biological material in a specification disclosure or the actual deposit of such material by an applicant or patent

owner does not create any presumption that such material is necessary to satisfy 35 U.S.C. 112 or that deposit in accordance with these regulations is or was required.

37 CFR 1.802(a) permits a deposit of a biological material to be referenced in a patent application where an invention is, or relies on, a biological material. The invention may rely on a biological material for the purposes of making or using the invention, either as a preferred mode or an alternative mode of operation. A reference to a deposit may be included in a specification even though the deposit is not required to satisfy the requirements of 35 U.S.C. 112.

There is no necessary implication or presumption that can or should be made about the need for a deposit simply because reference to a deposit is made in an application disclosure, as noted in paragraph (c). As noted in paragraph (b), biological material need not be deposited unless access to such material is necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112 and that access is not otherwise available in the absence of a deposit. Where a deposit is required to provide the necessary access, a deposit is acceptable for patent purposes only where it is made in accordance with these regulations. Even where access to biological material is required to satisfy these statutory requirements, a deposit may not be necessary if access sufficient to satisfy these requirements is otherwise available.

2404.01 Biological Material That Is Known and Readily Available to the Public

In an application where the invention required access to specific biological material, an applicant could show that the biological material is accessible because it is known and readily available to the public. The concepts of "known and readily available" are considered to reflect a level of public accessibility to a necessary component of an invention disclosure that is consistent with an ability to make and use the invention. To avoid the need for a deposit on this basis, the biological material must be both known and readily available – neither concept alone is sufficient. A material may be known in the sense that its existence has been published, but is not available to those who wish to obtain that particular known biological material. Likewise, a biological material may be available in the sense that those having possession of it would make it available upon request, but no one has been informed of its existence.

The Board of Patent Appeals and Interferences has held that a description of the precise geographic location of marine tunicates, as a biological material, used in a claimed invention was adequate to satisfy the enablement requirement of 35 U.S.C. 112. *Ex Parte Rinehart*,
10 USPQ2d 1719 (Bd Pat. App. & Int. 1985). The term "readily" used in the phrase "known and readily available" is considered appropriate to define that degree of availability which would be reasonable under the circumstances. If the biological material and its natural location can be adequately described so that one skilled in the art could obtain it using ordinary skill in the art, the disclosure would appear to be sufficient to meet the enablement requirement of 35 U.S.C. 112 without a deposit so long as its degree of availability is reasonable under the circumstances.

By showing that a biological material is known and readily available or by making a deposit in accordance with these rules, applicant does not guarantee that such biological material will be available forever. Public access during the term of the patent may affect the enforceability of the patent. Although there is a public interest in the availability of a deposited biological material during and after the period of enforceability of the patent, there should not be any undue concern about continued access to the public. Unless there is a reasonable basis to believe that the biological material will cease to be available during the enforceable life of the patent, current availability would satisfy the requirement. The incentives provided by the patent system should not be constrained by the mere possibility that a disclosure that was once enabling would become non–enabling over a period of time through no fault of the patentee. *In re Metcalfe*, 410 F.2d 1378, 161 USPQ 789 (CCPA 1969).

If an applicant has adequately established that a biological material is known and readily available, the Office will accept that showing. In those instances, however, the applicant takes the risk that the material may cease to be known and readily available. Such a defect cannot be cured by reissue after the grant of a patent.

On the other hand, *Ex parte Humphreys*, 24 USPQ2d 1255 (Bd Pat. App. & Int. 1992), held that the only manner in which applicants could satisfy their burden of assuring public access to the needed biological material, and, thereby, compliance with the enablement require-

ment of 35 U.S.C. 112, was by making an appropriate deposit. The fact that applicants and other members of the public were able to obtain the material in question from a given depository prior to and after the filing date of the application in issue did not establish that upon issuance of a patent on the application that such material would continue to be accessible to the public. The applicants did not make of record any of the facts and circumstances surrounding their access to the material in issue from the depository, nor was there any evidence as to the depository's policy regarding the material if a patent would have been granted. Further, there was no assurance that the depository would have allowed unlimited access to the material if the application had matured into a patent.

There are many factors that may be used as indicia that a biological material is known and readily available to the public. Relevant factors include commercial availability, references to the biological material in printed publications, declarations of accessibility by those working in the field, evidence of predictable isolation techniques, or an existing deposit made in accordance with these rules. Each factor alone may or may not be sufficient to demonstrate that the biological material is known and readily available. Those applicants that rely on evidence of accessibility other than a deposit take the risk that the patent may no longer be enforceable if the biological material necessary to satisfy the requirements of 35 U.S.C. 112 ceases to be accessible.

The Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material. A product could be commercially available but only at a price that effectively eliminates accessibility to those desiring to obtain a sample. The relationship between the applicant relying on a biological material and the commercial supplier is one factor that would be considered in determining whether the biological material was known and readily available. However, the mere fact that the biological material is commercially available only through the patent holder or the patent holder's agents or assigns shall not, by itself, justify a finding that the necessary material is not readily available, absent reason to believe that access to the biological material would later be improperly restricted.

The mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean that the deposited biological material is readily available. Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception, that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent. *Ex parte Hildebrand*, 15 USPQ2d 1662 (Bd Pat. App. & Int. 1990).

A Budapest Treaty deposit cited in a U.S. patent need not be made available if it was not required to satisfy 35 U.S.C. 112. Thus, a reference to a deposit will not be certified available unless either (1) the deposit was necessary to overcome a rejection under 35 U.S.C. 112, or (2) there is, in the record, a statement by the examiner that a rejection under 35 U.S.C. 112 would have been made "but for" the deposit (assumes deposit information in record, as filed). Otherwise, public access cannot be certified and the deposit cannot be relied upon for other purposes, e.g., the deposit cannot be relied upon by a third party to establish "known" and "readily available" in another application. See 37 CFR 1.808 and MPEP § 2410 and § 2410.02.

Once a deposit is made in a depository complying with these rules, and under conditions complying with these rules, a biological material will be considered to be readily available even though some requirement of law or regulation in the United States or in the country where the depository institution is located permits access to the material only under conditions imposed for health, safety or similar reasons. This provision is consistent with the Budapest Treaty (Article 5) and is designed to permit the patenting of inventions involving materials having restricted distribution, where the restrictions are imposed for the public, as opposed to the private, welfare.

2404.02 Biological Material That Can Be Made or Isolated Without Undue Experimentation

Applicant may show that a deposit is not necessary even though specific biological materials are required to practice the invention if those biological materials can be made or isolated without undue experimentation. Deposits may be required to support the claims if an isolation procedure requires undue experimentation to obtain the desired biological material. *Ex Parte Jackson*, 217

USPQ 804 (Bd App. 1982). No deposit is required, however, where the required biological materials can be obtained from publicly available material with only routine experimentation and a reliable screening test. *Tabuchi v. Nubel*, 559 F.2d 1183, 194 USPQ 521 (CCPA 1977); *Ex Parte Hata*, 6 USPQ2d 1652 (Bd Pat. App. & Int. 1987).

2404.03 Reference to a Deposit in the Specification

37 CFR 1.802(c) specifically provides that the mere reference to a biological material in the specification disclosure or the actual deposit of such material does not create any presumption that such referenced or deposited material is necessary to satisfy 35 U.S.C. 112, or that a deposit in accordance with these regulations is or was required. It should be noted, however, that a reference to a biological material, present in an application upon filing, may form the basis for making a deposit, where required, after the filing date of a given application but that the reference to the biological material, itself, cannot be added after filing without risking the prohibited introduction of new matter (35 U.S.C. 132). See the discussion of the Lundak application in MPEP § 2406.01.

2405 Acceptable Depository

37 CFR 1.803. Acceptable depository.

(a) A deposit shall be recognized for the purposes of these regulations if made in

(1) any International Depositary Authority (IDA) as established under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, or

(2) any other depository recognized to be suitable by the Office. Suitability will be determined by the Commissioner on the basis of the administrative and technical competence, and agreement of the depository to comply with the terms and conditions applicable to deposits for patent purposes. The Commissioner may seek the advice of impartial consultants on the suitability of a depository. The depository must:

(i) Have a continuous existence;

(ii) Exist independent of the control of the depositor;

(iii) Possess the staff and facilities sufficient to examine the viability of a deposit and store the deposit in a manner which ensures that it is kept viable and uncontaminated;

(iv) Provide for sufficient safety measures to minimize the risk of losing biological material deposited with it;

(v) Be impartial and objective;

(vi) Furnish samples of the deposited material in an expeditious and proper manner; and

(vii) Promptly notify depositors of its inability to furnish samples, and the reasons why.

(b) A depository seeking status under paragraph (a)(2) of this section must direct a communication to the Commissioner which shall:

(1) Indicate the name and address of the depository to which the communication relates;

(2) Contain detailed information as to the capacity of the depository to comply with the requirements of paragraph (a)(2) of this section, including information on its legal status, scientific standing, staff and facilities;

(3) Indicate that the depository intends to be available, for the purposes of deposit, to any depositor under these same conditions;

(4) Where the depository intends to accept for deposit only certain kinds of biological material, specify such kinds;

(5) Indicate the amount of any fees that the depository will, upon acquiring the status of suitable depository under paragraph (a)(2) of this section, charge for storage, viability statements and furnishings of samples of the deposit.

(c) A depository having status under paragraph (a)(2) of this section limited to certain kinds of biological material may extend such status to additional kinds of biological material by directing a communication to the Commissioner in accordance with paragraph (b) of this section. If a previous communication under paragraph (b) of this section is of record, items in common with the previous communication may be incorporated by reference.

(d) Once a depository is recognized to be suitable by the Commissioner or has defaulted or discontinued its performance under this section, notice thereof will be published in the Official Gazette of the Patent and Trademark Office.

37 CFR 1.803 indicates that a depository will be recognized as acceptable for the purposes of these regulations if it is either an International Depository Authority (IDA) established under the Budapest Treaty, or if it is a depository recognized as suitable by the Commissioner. After the effective date of these regulations, a deposit of biological material which is made in a depository which is not recognized as acceptable under this regulation will not be considered as satisfying the requirements of 35 U.S.C. 112. See *Ex parte Humphreys*, 24 USPQ2d 1255 (Bd Pat. App. & Int. 1992). On the other hand, if a deposit is not required to satisfy the requirements of 35 U.S.C. 112, it is permissible to make reference to such a deposit even though it may not be in a depository or made under the conditions which are acceptable under these regulations. As new depositories are recognized as suitable by the Commissioner, their identity will be announced in the *Official Gazette*.

An organization may be recognized as suitable by the Office if the procedure and conditions specified in 37 CFR 1.803(a)(2) and 37 CFR 1.803(b) are followed. Generally, it is not the intention of the Office to recognize as suitable any organization where the need for a suitable depository for patent purposes is being met by depositories recognized as IDAs under the Budapest Treaty. Suitability will be judged by the Commissioner, based on need and the information supplied by the orga-

nization seeking status, and information obtained from other sources that may be consulted.

While there is a desire to provide flexibility to a patent applicant in selecting an appropriate depository, these rules are not intended to permit each patent applicant to become its own depository since both the patent owner and the public have an interest in the continued availability and accessibility of the deposit during the enforceable life of the patent, and the public has a continuing interest in its availability when the patent is no longer enforceable. The concept of a depository independent of the control of the depositor or an IDA as an acceptable depository is based on the need and desire to ensure the safe and reliable storage of a deposited biological material under circumstances that are substantially free of the opportunity for intentional mishandling or negligent handling of the deposited material. The use of an independent depository or internationally recognized depository will tend to preserve the integrity of the deposit process against those that may accidentally alter the deposited material, may wish to tamper with the deposited material or may wish to resume control of its availability when the patent is no longer enforceable, and will tend to preserve the interest of the public in the access to the biological material once the term of the patent expires.

When a depository having status under 37 CFR 1.803(a)(2) seeks to change the kinds of biological materials that it will accept and maintain for the purposes of these rules, a communication requesting such a change should be directed to the Commissioner containing the information requested in 37 CFR 1.803(b). When such a change is requested, the requesting depository should provide a complete list of the kinds of biological materials it will accept.

37 CFR 1.803(d) indicates that once a depository is recognized as suitable for the purposes of this rule, or has defaulted or discontinued its performance under this section, notice thereof will be published in the *Official Gazette* of the Patent and Trademark Office. A current list (as of January, 1998) of IDAs recognized under the Budapest Treaty, with addresses, is included below. The mere fact that a deposit has been made in one of these depositories does not mean that the terms of the deposit meet either the requirements of the Budapest Treaty or the deposit regulations. Many of the depositories recognized under the Budapest Treaty have many different arrangements under which biological material may be stored.

The World Intellectual Property Organization (WIPO) publishes a Guide to the Deposit of Micro-organisms under the Budapest Treaty (WIPO Publication No. 661 (E)) on the procedures and requirements concerning the deposit of biological material, including procedures for obtaining a sample of deposited material, in each of the international depository authorities.

CURRENT IDAs

The following constitutes the list of IDAs recognized under the Budapest Treaty. The list is current as of January, 1998.

Advanced Biotechnology Center (ABC)
Interlab Cell Line Collection
(Biotechnology Dept.)
Largo Rossana Benzi, 10
16132 Genova
Italy

Agricultural Research Service
Culture Collection (NRRL)
1815 North University Street
Peoria, Illinois 61604
USA

All-Russian Scientific Center of Antibiotics (VNIIA)
Nagatinskaya Street 3-a
Moscow 113105
Russian Federation

American Type Culture Collection (ATCC)
10801 University Blvd.
Manassas, Virginia 20110-2209
USA

Australian Government Analytical
Laboratories (AGAL)
The New South Wales Regional Laboratory
1, Suakin Street
Pymble, NSW 2073
Australia

Belgian Coordinated Collections of
Microorganisms (BCCM)
Prime Minister's Services
Federal Office for Scientific, Technical and
Cultural Affairs (OSTC)

Rue de la Science 8
B−1000 Brussells
Belgium

Centraalbureau Voor Schimmelcultures (CBS)
Oosterstraat 1
Postbus 273
NL−3740 AG Baarn
Netherlands

China Center for Type Culture Collection (CCTCC)
Wuhan University
Wuhan 430072
China

China General Microbiological Culture Collection Center (CGMCC)
China Committee for Culture Collection of Microorganisms
P.O. Box 2714
Beijing 100080
China

Coleción Española de Cultivos Tipo (CECT)
Universidad de Valencia
Edificio de Investigación
Campus de Burjasot
46100 Burjasot (Valencia)
Spain

Collection Nationale De Cultures
De Microorganismes (CNCM)
Institut Pasteur
28, rue du Dr Roux
75724 Paris Cédex 15
France

Collection of Industrial Yeasts (DBVPG)
Applied Microbiology Section
Department of Plant Biology
Faculty of Agriculture
University of Perugia
Borgo 20 Giugno, 74
06122 Perugia
Italy

Culture Collection of Algae and Protozoa (CCAP)
Institute of Freshwater Ecology
Windermere Laboratory
Ambleside, Cumbria LA22 0LP
United Kingdom and Dunstaffnage Marine Laboratory
P.O. Box 3
Oban, Argyll PA34 4AD
United Kingdom

Culture Collection of Yeasts (CCY)
Institute of Chemistry
Slovak Academy of Sciences
Dúbravská cesta 9
842 38 Bratislava,
Slovakia

Czech Collection of Microorganisms (CCM)
Masaryc University
ul. Tvrdého č. 14
602 00 Brno
Czech Republic

DSMZ−Deutsche Sammlung Von Mikroorganismen und Zellkulturen GmbH (DSMZ)
Mascheroder Weg 1b
D−38124 Braunschweig
Germany

European Collection of Cell Cultures (ECACC)
Vaccine Research and Production Laboratory
Public Health Laboratory Service
Centre for Applied Microbiology and Research
Porton Down
Salisbury, Wiltshire SP4 0JG
United Kingdom

International Mycological Institute (IMI)
Bakeham Lane
Englefield Green
Egham, Surrey TW20 9TY
United Kingdom

Korea Research Institute of Bioscience and Biotechnology (KRIBB)
52, Oun−Dong
Yusong−Ku
Taejon 305−333
Republic of Korea

Korean Cell Line Research Foundation (KCLRF)
Cancer Research Institute
Seoul National University College of Medicine
28 Yungon−dong, Chongno−gu
Seoul 110−799
Republic of Korea

Korean Culture Center of Microorganisms (KCCM)
College of Engineering
Yonsei University
Sodaemun gu
Seoul 120–749
Republic of Korea

Microbial Strain Collection of Latvia (MSCL)
University of Latvia
Faculty of Biology
Blvd. Kronvalda 4
LV–1586 Riga
Latvia

National Bank for Industrial Microorganisms and Cell Cultures (NBIMCC)
125, Tsarigradskochausse Blvd.
Block 2
1113 Sofia
Bulgaria

National Collection of Agricultural and Industrial Microorganisms (NCAIM)
Department of Microbiology and Biotechnology
University of Horticulture and the Food Industry
Somlói út 14–16
H–1118 Budapest
Hungary

National Collection of Type Cultures (NCTC)
Central Public Health Laboratory
61 Colindale Avenue
London, NW9 5HT
United Kingdom

National Collection of Yeast Cultures (NCYC)
AFRC Institute of Food Research
Norwich Laboratory
Colney Lane
Norwich NR4 7UA
United Kingdom

National Collections of Industrial and Marine Bacteria Limited (NCIMB)
23 St. Machar Drive
Aberdeen AB2 1RY
Scotland
United Kingdom

National Institute of Bioscience and Human–Technology (NIBH)
Agency of Industrial Science and Technology
Ministry of International Trade and Industry
1–3, Higashi 1–chome
Tsukuba–shi
Ibaraki–ken 305
Japan

Russian Collection of Microorganisms (VKM)
Prospekt Naouki, 5
142292 Puschino (Moscow Region)
Russian Federation

Russian National Collection of Industrial Microorganisms (VKPM)
GNII Genetika
Dorozhny proezd. 1
Moscow 113545
Russian Federation

2406 Time of Making an Original Deposit

37 CFR 1.804. Time of making an original deposit.

(a) Whenever a biological material is specifically identified in an application for patent as filed, an original deposit thereof may be made at any time before filing the application for patent or, subject to § 1.809, during pendency of the application for patent.

(b) When the original deposit is made after the effective filing date of an application for patent, the applicant must promptly submit a statement from a person in a position to corroborate the fact, stating that the biological material which is deposited is a biological material specifically identified in the application as filed.

37 CFR 1.804 specifies the time for making an original deposit to fulfill the requirements of 35 U.S.C. 112. For the reasons discussed throughout this section, it is recommended that a deposit be made before the filing date of the application. However, for the purposes of complying with the requirements of 35 U.S.C. 112, a deposit of a biological material may be made at any time before filing the application for patent or during the pendency of the application subject to the conditions of 37 CFR 1.809. Where a deposit is needed to satisfy the requirements of 35 U.S.C. 112 and it is made during the pendency of the application, it must be made no later than the time period set by the examiner at the time the Notice of Allowance and Issue Fee Due is mailed. A necessary deposit need not be made by an applicant until the application is in condition for allowance so long as the applicant provides a written assurance that an acceptable deposit will be made on or before the payment of the issue fee. This written assurance must provide sufficiently detailed in-

formation to convince the examiner that there is no outstanding issue regarding deposits that needs to be resolved.

These rules are equally applicable in the cases of international and national stage applications filed under the Patent Cooperation Treaty. Insofar as the rules do not permit post–issuance original deposits, the failure to make an original deposit in an application cannot be cured by filing a reissue application or instituting a reexamination proceeding. However, if an amendment of claims in a reexamination proceeding raises the need for a deposit, an original deposit may be made during the reexamination proceeding.

2406.01 Description in Application Specification

37 CFR 1.804(a) specifies not only a permissible time frame for making an original deposit, but also specifies that the biological material deposited must be specifically identified in the application for patent as filed. The requirement for a specific identification is consistent with the description requirement of the first paragraph of 35 U.S.C. 112 and provides an antecedent basis for the biological material which either has been or will be deposited before the patent is granted.

The description in the Lundak application as filed (now patent 4,594,325) provides a suitable illustration of the specific identification and description which are required in an application as filed. In that application, an immortal B–cell line was disclosed and claimed. The cell line was referred to in the application, as filed, as WI–L2–729 HF2. The methods of obtaining and using this cell line were also described in the application as filed. A deposit of the cell line was made with the American Type Culture Collection (ATCC) about a week after the application was filed in the United States. The United States Court of Appeals for the Federal Circuit held that the requirements of access by the Office to a sample of the cell line during pendency, and public access after grant, were met by Lundak's procedures. The Court further held that the addition of information designating the depository, accession number, and deposit date of the deposited cell line in ATCC after the filing date did not violate the prohibition against new matter in 35 U.S.C. 132. *In re Lundak*, 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985). However, it must be clear from the application as filed that the invention claimed and described in the specification "was fully capable of being reduced to practice (i.e., no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remained in order to obtain an operative, useful process)." *Feldman v. Aunstrup*, 517 F.2d 1351, 1355, 186 USPQ 108, 113 (CCPA 1975), *cert. denied*, 424 U.S. 912 (1976).

2406.02 Deposit After Filing Date – Corroboration

When the original deposit is made after the effective filing date of an application for patent, an applicant is required to promptly submit a statement from a person in a position to corroborate that the biological material which is deposited is a biological material specifically identified in the application (the filing date of which is relied upon) as filed. The nature of this corroboration will depend on the circumstances in the particular application under consideration, including the length of time between the application filing date and the date of deposit. While few, if any, situations can be imagined where the description requirement of 35 U.S.C. 112 can be satisfied where the biological material was not in existence at the time of filing, the rules will not preclude such a situation as there is no requirement in the patent law that an actual reduction to practice occur as a condition precedent to filing a patent application.

2406.03 Possible Loss of U.S. Filing Date in Other Countries

Those applicants intending to file patent applications in a country foreign to the United States relying upon biological material that must be deposited to satisfy the requirements of 35 U.S.C. 112 when the application is filed in the United States are cautioned that in many countries the deposit must be made before the filing date of the priority application in order to obtain foreign priority rights. Thus, while the deposit of a biological material subsequent to the effective filing date of a United States application is sufficient to comply with 35 U.S.C. 112, an applicant may not be able to rely on the filing date of such a U.S. application if a patent is sought in certain countries foreign to the United States.

2407 Replacement or Supplement of Deposit

37 CFR 1.805. Replacement or supplement of deposit.

(a) A depositor, after receiving notice during the pendency of an application for patent, application for reissue patent or reexamination

proceeding, that the depository possessing a deposit either cannot furnish samples thereof or can furnish samples thereof but the deposit has become contaminated or has lost its capability to function as described in the specification, shall notify the Office in writing, in each application for patent or patent affected. In such a case, or where the Office otherwise learns, during the pendency of an application for patent, application for reissue patent or reexamination proceeding, that the depository possessing a deposit either cannot furnish samples thereof or can furnish samples thereof but the deposit has become contaminated or has lost its capability to function as described in the specification, the need for making a replacement or supplemental deposit will be governed by the same considerations governing the need for making an original deposit under the provisions set forth in § 1.802(b). A replacement or supplemental deposit made during the pendency of an application for patent shall not be accepted unless it meets the requirements for making an original deposit under these regulations, including the requirement set forth under § 1.804(b). A replacement or supplemental deposit made in connection with a patent, whether or not made during the pendency of an application for reissue patent or a reexamination proceeding or both, shall not be accepted unless a certificate of correction under § 1.323 is requested by the patent owner which meets the terms of paragraphs (b) and (c) of this section.

(b) A request for certificate of correction under this section shall not be granted unless the certificate identifies:

(1) The accession number for the replacement or supplemental deposit;

(2) The date of the deposit; and

(3) The name and address of the depository.

(c) A request for a certificate of correction under this section shall not be granted unless the request is made promptly after the replacement or supplemental deposit has been made and the request:

(1) Includes a statement of the reason for making the replacement or supplemental deposit;

(2) Includes a statement from a person in a position to corroborate the fact, and stating that the replacement or supplemental deposit is of a biological material which is identical to that originally deposited;

(3) Includes a showing that the patent owner acted diligently — —

(i) In the case of a replacement deposit, in making the deposit after receiving notice that samples could no longer be furnished from an earlier deposit; or

(ii) In the case of a supplemental deposit, in making the deposit after receiving notice that the earlier deposit had become contaminated or had lost its capability to function as described in the specification;

(4) Includes a statement that the term of the replacement or supplemental deposit expires no earlier than the term of the deposit being replaced or supplemented; and

(5) Otherwise establishes compliance with these regulations.

(d) A depositor s failure to replace a deposit, or in the case of a patent, to diligently replace a deposit and promptly thereafter request a certificate of correction which meets the terms of paragraphs (b) and (c) of this section, after being notified that the depository possessing the deposit cannot furnish samples thereof, shall cause the application or patent involved to be treated in any Office proceeding as if no deposit were made.

(e) In the event a deposit is replaced according to these regulations, the Office will apply a rebuttable presumption of identity between the original and the replacement deposit where a patent making reference to the deposit is relied upon during any Office proceeding.

(f) A replacement or supplemental deposit made during the pendency of an application for patent may be made for any reason.

(g) In no case is a replacement or supplemental deposit of a biological material necessary where the biological material, in accordance with § 1.802(b), need not be deposited.

(h) No replacement deposit of a biological material is necessary where a depository can furnish samples thereof but the depository for national security, health or environmental safety reasons is unable to provide samples to requesters outside of the jurisdiction where the depository is located.

(i) The Office will not recognize in any Office proceeding a replacement deposit of a biological material made by a patent owner where the depository could furnish samples of the deposit being replaced.

37 CFR 1.805 relates to the deposit of a biological material to replace or supplement a previous deposit. The term "replacement" is directed to those situations where one deposit is being substituted for another. An applicant may have greater latitude in replacing a deposit during the pendency of an application than after the patent is granted. Replacement will typically take place where the earlier deposit is no longer viable. The term "supplement" is directed to those situations where the earlier deposit is still viable in the sense that it is alive and capable of replication either directly or indirectly, but has lost a quality (e.g., purity, functionality) it allegedly possessed at the time the application was filed. The procedures in these rules contemplate that only the original depositor would have a right to replace or supplement the original deposit.

2407.01 In a Pending Application

37 CFR 1.805(a) relates to the procedure for replacing or supplementing a deposit with respect to a pending application or a patent. An applicant or patent owner is required to notify the Office when it obtains information that the depository possessing a deposit cannot furnish samples of the deposit to satisfy the requirements of 35 U.S.C. 112. When the Office is so informed or otherwise becomes aware that samples of the deposited material cannot be furnished by the depository, the examiner will treat the application or reexamination proceeding, whichever is applicable, as if no deposit existed. A replacement or supplemental deposit will be accepted if it meets all the requirements for making an original deposit.

It should be noted that in a pending application, an applicant need not replace the identical material previously deposited, but may make an original deposit of a biological material which is specifically identified and described in the application as filed. Whether this alterna-

tive deposit will meet the requirements of 35 U.S.C. 112 with respect to the claimed subject matter must be resolved by the examiner on a case–by–case basis. The conditions in 37 CFR 1.802(b) and 37 CFR 1.804 (b) must be satisfied.

2407.02 After a Patent Has Issued

A replacement deposit made in connection with an application for reissue patent or a reexamination proceeding or both shall not be accepted unless a certificate of correction is requested which meets the terms of 37 CFR 1.805(b) and 37 CFR 1.805 (c) for replacement deposits. Any correction made to the original patent will be automatically incorporated into the reissued or reexamined patent unless changes are made during examination of the reissue application or reexamination proceeding.

37 CFR 1.805(b) and 37 CFR 1.805(c) specify the procedures that a patent owner may follow to ensure that a patent contains the appropriate information about a deposited biological material in the event that a replacement or supplemental deposit is made after the patent is granted. 37 CFR 1.805(b) describes the information which must be contained in the certificate of correction, whereas 37 CFR 1.805(c) describes the information which must be provided in the request to make the correction.

2407.03 Failure to Replace

37 CFR 1.805(d) sets forth the Office position that the failure to make a replacement deposit in a case pending before the Office, for example a reissue or reexamination proceeding, where a deposit is considered to be necessary to satisfy the requirements of 35 U.S.C. 112, shall cause the application or patent involved to be treated in any Office proceeding as if no deposit were made. The provisions of 37 CFR 1.805(g) indicate that a replacement need not be made where, at the point in time when replacement would otherwise be necessary, access to the necessary biological material was otherwise available. For example, a replacement deposit would not be required under the circumstances where access to the necessary biological material was established through commercial suppliers.

2407.04 Treatment of Replacement

37 CFR 1.805(e) indicates that the Office will apply a rebuttable presumption of identity between the replacement deposit and an original deposit where a patent making reference to the deposit is relied on during any Office proceeding. This means that where a replacement deposit is permitted and made, the examiner will assume that the same material as described in the patent is accessible from the identified depository unless evidence to the contrary comes to the attention of the Office.

An applicant for patent may make a replacement deposit during the pendency of the application for any reason. The provisions of 37 CFR 1.805(f) recognize that since an original deposit may be made during the pendency of the application subject to the conditions of 37 CFR 1.809, a replacement deposit logically cannot be held to any higher standard or any further requirements.

2407.05 Exemption From Replacement

The provisions of 37 CFR 1.805(h) indicate that a replacement deposit is not required even though the depository cannot furnish samples, under certain conditions, to those requesting a sample outside of the jurisdiction where the depository is located. The conditions are specified in this paragraph as being limited to national security, health or environmental safety reasons.

2407.06 Replacement May Not Be Recognized

Finally, 37 CFR 1.805(i) indicates that the Office will not recognize in any Office proceeding a replacement deposit made by the patent owner where the depository could furnish samples of the original deposit being replaced. The best evidence of what was originally deposited should not be lost through destruction or replacement if made in association with an existing patent. A supplemental deposit may be accepted in an Office proceeding, however, depending on the circumstances in each case.

2408 Term of Deposit

37 CFR 1.806. Term of deposit.

A deposit made before or during pendency of an application for patent shall be made for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the depository. In any case, samples must be stored under agreements that would make them available beyond the enforceable life of the patent for which the deposit was made.

The term of deposit must satisfy the requirements of the Budapest Treaty which sets a term of at least 30 years

from the date of deposit and at least 5 years after the most recent request for the furnishing of a sample of the deposit was received by the depository. In the event that the 30–year term covers the 17–year term or 20–year term of the patent plus 6 years to include the Statute of Limitations, no further requirement is necessary. Unless applicant indicates that the deposit has been made under the Budapest Treaty, applicant must indicate the term for which the deposit has been made. The mere possibility of patent term extension or extended litigation involving the patent should not be considered in this analysis.

In the event that the 30–year term of deposit measured from the date of deposit would necessarily terminate within the period of enforceability of the patent (the normal 17–year term or 20–year term plus 6 years to include the Statute of Limitations), samples must be stored under agreements that would make them available beyond the enforceable life of the patent (i.e., until 23 years after issuance or 26 years after application filing) for which the deposit was made. No requirement should be made as to any particular period of time beyond the enforceable life of the patent. The purpose of the requirement is to insure that a deposited biological material necessary for the practice of a patented invention would be available to the public after expiration of the patent for which the deposit was made. The term of the deposit must comply with the requirements of each sentence of 37 CFR 1.806 whether or not the deposit is made under the Budapest Treaty. A specific statement that the deposit complies with the second sentence of this section is required only where the 30–year term would terminate within the enforceable life of the patent.

2409 Viability of Deposit

37 CFR 1.807. Viability of deposit.

(a) A deposit of biological material that is capable of self–replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. No evidence is necessarily required regarding the ability of the deposited material to perform any function described in the patent application.

(b) A viability statement for each deposit of a biological material defined in paragraph (a) of this section not made under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure must be filed in the application and must contain:

(1) The name and address of the depository;

(2) The name and address of the depositor;

(3) The date of deposit;

(4) The identity of the deposit and the accession number given by the depository;

(5) The date of the viability test;

(6) The procedures used to obtain a sample if the test is not done by the depository; and

(7) A statement that the deposit is capable of reproduction.

(c) If a viability test indicates that the deposit is not viable upon receipt, or the examiner cannot, for scientific or other valid reasons, accept the statement of viability received from the applicant, the examiner shall proceed as if no deposit has been made. The examiner will accept the conclusion set forth in a viability statement issued by a depository recognized under § 1.803(a).

37 CFR 1.807 requires that the deposit of biological material that is capable of self–replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. This requirement for viability is essentially a requirement that the deposited material is capable of reproduction. For the purpose of making a deposit under these rules, there is no requirement that evidence be provided that the deposited material is capable or has the ability to perform any function described in the patent application. However, as with any other issue of description or enablement, if the examiner has evidence or reason to question the objective statements made in the patent application, applicants may be required to demonstrate that the deposited biological material will perform in the manner described.

Under the Budapest Treaty, there is a requirement that the deposit be tested for viability before it is accepted. Thus, a mere statement by an applicant, an authorized representative of applicant or the assignee that the deposit has been accepted under the Budapest Treaty would satisfy 37 CFR 1.807.

For each deposit which is not made under the Budapest Treaty, a viability statement must be filed in the patent application and contain the information listed in paragraph (b) of this section. Under 37 CFR 1.807(c), the examiner will accept the conclusion set forth in a viability statement which is issued by a depository recognized under 37 CFR 1.803(a). If the viability test indicates that the deposit is not viable upon receipt, or the examiner cannot, for scientific or other valid reasons, accept the statement of viability received from the applicant, the examiner shall so notify the applicant stating the reasons for not accepting the statement and proceed

with the examination process as if no deposit had been made.

2410 Furnishing of Samples

37 CFR 1.808. Furnishing of samples.

(a) A deposit must be made under conditions that assure that:

(1) Access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Commissioner to be entitled thereto under § 1.14 and 35 U.S.C. 122, and

(2) Subject to paragraph (b) of this section, all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent.

(b) The depositor may contract with the depository to require that samples of a deposited biological material shall be furnished only if a request for a sample, during the term of the patent:

(1) Is in writing or other tangible form and dated;

(2) Contains the name and address of the requesting party and the accession number of the deposit; and

(3) Is communicated in writing by the depository to the depositor along with the date on which the sample was furnished and the name and address of the party to whom the sample was furnished.

(c) Upon request made to the Office, the Office will certify whether a deposit has been stated to have been made under conditions which make it available to the public as of the issue date of the patent grant provided the request contains:

(1) The name and address of the depository;

(2) The accession number given to the deposit;

(3) The patent number and issue date of the patent referring to the deposit; and

(4) The name and address of the requesting party.

2410.01 Conditions of Deposit

37 CFR 1.808 requires that the deposit of biological material be made under two conditions:

(A) access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 U.S.C. 122, and

(B) with one exception, that all restrictions imposed by the depositor on the availability to the public of the deposited biological material be irrevocably removed upon the granting of the patent.

The one exception that is permitted is specified in 37 CFR 1.808(b)which permits the depositor to contract with the depository to require that samples of a deposited biological material shall be furnished only if a request for a sample, during the term of the patent, meets any one or all of the three conditions specified in this paragraph. These conditions are:

(A) the request is in writing or other tangible form and dated; and/or

(B) the request contains the name and address of the requesting party and the accession number of the deposit; and/or

(C) the request is communicated in writing by the depository to the depositor along with the date on which the sample was furnished and the name and address of the party to whom the sample was furnished.

It should be noted that this exception to the general rule that all restrictions will be removed must be strictly followed and that no variations of this explicit exception will be accepted as meeting the conditions of this section. Although this exception is consistent with the provisions in the Budapest Treaty and its implementing regulations (Rule 11.4), other conditions on accessibility are permitted under the Budapest Treaty as prescribed by national law. Consequently, the mere indication that a deposit has been made under conditions prescribed by the Budapest Treaty would satisfy all conditions of these regulations except the requirement that all restrictions on access be removed on grant of the patent. *Ex parte Hildebrand*, 15 USPQ2d 1662 (Bd Pat. App. & Int. 1990).

2410.02 Certification of Accessibility of Deposit

Since the mere description of a deposit or identity of a deposit in a patent specification is not necessarily an indication that a requirement for deposit was made or that a deposit which complies with these rules has been made, accessibility to a deposited material referenced in a patent may depend on the satisfaction of conditions not apparent on the face of the patent. For these reasons, and upon request made to the Patent and Trademark Office, the Office will certify whether a deposit has been stated to have been made under conditions which would make it available to the public as of the issue date of the patent grant provided the request is made to the Director of Patent Examining Group 1640 or 1650, and contains the following information:

(A) the name and address of the depository;

(B) the accession number given to the deposit;

(C) the patent number and issue date of the patent referring to the deposit; and

(D) the name and address of the requesting party.

For those deposits made pursuant to the Budapest Treaty, the World Intellectual Property Organization provides a form (Form BP–12) for requesting a certification of the availability of samples of deposited microorganisms pursuant to Rule 11.3(a) of the Regulations under the Budapest Treaty. Copies of this form are available from the Director of Patent Examining Group 1640 or 1650.

2411 Examination Procedures

37 CFR 1.809. Examination procedures.

(a) The examiner shall determine pursuant to § 1.104 in each application for patent, application for reissue patent or reexamination proceeding if a deposit is needed, and if needed, if a deposit actually made is acceptable for patent purposes. If a deposit is needed and has not been made or replaced or supplemented in accordance with these regulations, the examiner, where appropriate, shall reject the affected claims under the appropriate provision of 35 U.S.C. 112, explaining why a deposit is needed and/or why a deposit actually made cannot be accepted.

(b) The applicant for patent or patent owner shall respond to a rejection under paragraph (a) of this section by—

(1) In the case of an applicant for patent, making an acceptable original or replacement or supplemental deposit or assuring the Office in writing that an acceptable deposit will be made on or before the date of payment of the issue fee, or, in the case of a patent owner, requesting a certificate of correction of the patent which meets the terms of paragraphs (b) and (c) of § 1.805, or

(2) Arguing why a deposit is not needed under the circumstances of the application or patent considered and/or why a deposit actually made should be accepted. Other replies to the examiner's action shall be considered non–responsive. The rejection will be repeated until either paragraph (b) (1) of this section is satisfied or the examiner is convinced that a deposit is not needed.

(c) If an application for patent is otherwise in condition for allowance except for a needed deposit and the Office has received a written assurance that an acceptable deposit will be made on or before payment of the issue fee, the Office will mail to the applicant a Notice of Allowance and Issue Fee Due together with a requirement that the needed deposit be made within three months. The period for satisfying this requirement is extendible under § 1.136. Failure to make the needed deposit in accordance with this requirement will result in abandonment of the application for failure to prosecute.

(d) For each deposit made pursuant to these regulations, the specification shall contain:

(1) The accession number for the deposit;

(2) The date of the deposit;

(3) A description of the deposited biological material sufficient to specifically identify it and to permit examination; and

(4) The name and address of the depository.

37 CFR 1.809 sets forth procedures that will be used by the examiner to address a deposit issue. The burden is initially on the Office to establish that access to a biological material is necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112. Once the Office has met this burden, the burden shifts to the applicant or patent owner to demonstrate that access to such biological material either is not necessary, or is already available, or that a deposit of such material will be made in accordance with these regulations.

2411.01 Rejections Based on Deposit Issue

Under 37 CFR 1.809(a), once the examiner has determined that access to a biological material is necessary, and there is no information that would support the conclusion that access is currently available in accordance with these regulations, the examiner should make an appropriate rejection under 35 U.S.C. 112 until such time as a deposit in accordance with these regulations is actually made or a written assurance is received in the patent application that such a deposit will be made upon an indication of allowability of the application. The examiner should clearly indicate the statutory basis for the rejection and the reasons that are relied upon by the examiner to conclude that the application does not comply with some requirement of 35 U.S.C. 112. Although not exhaustive, the following grounds of rejection may be applicable in appropriate circumstances:

(A) 35 U.S.C. 112, first paragraph – lack of an enabling disclosure without access to a specific biological material. This ground of rejection should be accompanied by evidence of scientific reasoning to support the conclusion that a person skilled in the art could not make or use the invention defined in and commensurate with the claims without access to the specific biological material.

(B) 35 U.S.C. 112, first paragraph – description requirement. This ground of rejection typically arises in the context that the application as filed does not contain a description to support an amendment to the specification or claims. An amendment to the claims that is not described in the application as filed would justify a rejection of the affected claims under 35 U.S.C. 112, first paragraph. If an amendment is made to the application, other than the claims, that is not described in the application as filed, this would justify an objection under 35 U.S.C. 112, first paragraph and/or 35 U.S.C. 132 (prohibition against the introduction of new matter) and a requirement that the amendment be canceled.

(C) 35 U.S.C. 112, first paragraph – best mode requirement. This ground of rejection will be rare in the *ex parte* examination process because it requires (1) a

finding by the examiner that, at the time the application was filed, the inventor(s) knew of a specific material that was considered by the inventor(s) to be better than any other, and (2) if a best mode was contemplated at that time, that the inventor(s) concealed the best mode (accidentally or intentionally) by failing to adequately describe that best mode. See *Chemcast Corp. v. Arco Industries Corp.*, 913 F.2d 923, 16 USPQ2d 1033 (Fed. Cir. 1990). The Court of Appeals for the Federal Circuit has at least twice resolved a best mode issue arising in the context of a biotechnology invention in favor of the patentee. See *Scripps Clinic and Research Foundation v. Genentech Inc.*, 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991) with respect to monoclonal antibodies, and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) with respect to mammalian host cells.

(D) 35 U.S.C. 112, second paragraph – indefiniteness. This ground of rejection, as applied to a deposit issue, requires the examiner to provide reasons why the terms in the claims and/or scope of the invention are unclear because of an incomplete or inaccurate description or the absence of a reference to a biological material.

(E) 35 U.S.C. 112, second paragraph – claims do not set forth what applicants regard as their invention. This ground of rejection requires the citation of some evidence, not contained in the application as filed, that the claims do not set forth what applicants regard as their invention. *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969). Any disagreement between the content of the application disclosure and the scope of the claims should be addressed under 35 U.S.C. 112, first paragraph. See *In re Ehrreich*, 590 F.2d 902, 200 USPQ 504 (CCPA 1979).

Where a deposit is required to satisfy 35 U.S.C. 112, a deposit must be made in accordance with these regulations. A deposit accepted in any IDA under the Budapest Treaty shall be accepted for patent purposes if made under conditions which comply with 37 CFR 1.806 and 37 CFR 1.808(a) concerning term of deposit and permissible conditions on access once the patent is granted.

2411.02 Replies to Rejections Based on Deposit Issue

Once a rejection under 35 U.S.C. 112 has been made by the examiner directed to the absence of access to a biological material, applicant may reply, pursuant to 37 CFR 1.809 (b)(1), by either making an acceptable original or replacement deposit in accordance with these regulations, or assuring the Office in writing that an acceptable deposit will be made on or before the date of payment of the issue fee, or by submitting an argument of why a deposit is not required under the circumstances of the application being considered. Other replies to such a rejection by the examiner shall be considered nonresponsive and may result in abandonment of the application. The rejection will be repeated and made final until the requirements of 37 CFR 1.809(b)(1) are satisfied or the examiner is convinced that a deposit is not required for the claimed subject matter. Once the rejection is made final, the requirements of 37 CFR 1.116 apply to further submissions. The written assurance will be accepted by the Office if it clearly states that an acceptable deposit will be made within the required time and under conditions which satisfy these rules. In the case that an acceptable written assurance has been made by the applicant, the rejection under 35 U.S.C 112 directed to the absence of access to the biological material should be removed.

2411.03 Application in Condition for Allowance Except for Deposit

As set forth in 37 CFR 1.809(c), in the event that an application for patent is otherwise in condition for allowance except for a required deposit and the Office has received a written assurance that an acceptable deposit will be made, the Office will mail to the applicant a requirement that the required deposit be made within 3 months together with the Notice of Allowance and Issue Fee Due. Although the period for paying the issue fee cannot be extended under the provisions of 37 CFR 1.136, the period for satisfying the requirement to make an acceptable deposit may be extended under the provisions of that section. Failure to make the needed deposit in accordance with this requirement may be considered a failure to prosecute the application under 35 U.S.C. 133 and result in abandonment of the application. Once the deposit has been made, information regarding the deposit, such as the name of the depository, the accession number and the date of the deposit, that is to be added to the specification must be added by means of filing an amendment under the provisions of 37 CFR 1.312. A petition and fee are required if the 37 CFR 1.312 amendment is filed after the issue fee has been paid.

2411.04 After a Patent Has Been Granted

In a proceeding involving a patent, it may not be possible to request a certificate of correction of the patent which meets the terms of 37 CFR 1.805(b) and 37 CFR 1.805(c). For example, if the patent owner is on notice that samples of an original deposit can no longer be furnished by the depository, failure to diligently make a replacement deposit will preclude grant of a certificate of correction. A replacement deposit subsequently made will not be recognized by the Office nor will a request for certificate of correction, even if made promptly thereafter, be granted. It would also not be possible to request a certificate of correction of the patent which meets the terms of 37 CFR 1.805(b) and 37 CFR 1.805(c) where no original deposit was made before or during the pendency of the application which matured into the patent.

A patent defective because of lack of a necessary deposit is necessarily fatally defective for failure to comply with the first paragraph of 35 U.S.C. 112. Reissue is not available in such cases. See *In re Hay*, 534 F.2d 917, 189 USPQ 790 (CCPA 1976). Whether reissue is available where a biological material necessary for compliance with 35 U.S.C. 112 was known and readily available at the time of issuance of the patent and subsequently ceased to be readily available is problematic. Nevertheless, the rules do not provide for post-issuance original deposits.

Where an applicant for patent has any doubt as to whether access to a biological material specifically identified in the specification is necessary to satisfy 35 U.S.C. 112 or whether such a material, while currently freely available, may become unavailable in the future, the applicant would be well-advised to make a deposit thereof before any patent issues. Similarly, where a patent owner has any doubt whether a deposit referred to in the specification is a biological material necessary to satisfy 35 U.S.C. 112 and, if the material is necessary, whether it is otherwise known and readily available, the patent owner would be well-advised to follow the procedures set forth in 37 CFR 1.805(b) and 37 CFR 1.805(c) after receiving the notice specified in those paragraphs.

2411.05 Content of Application with Respect to Deposited Material

37 CFR 1.809(d) sets forth the requirements for the content of the specification with respect to a deposited biological material. Specifically, the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited biological material sufficient to specifically identify it and to permit examination. The description also must be sufficient to permit verification that the deposited biological material is in fact that disclosed. Once the patent issues, the description must be sufficient to aid in the resolution of questions of infringement. As a general rule, the more information that is provided about a particular deposited biological material, the better the examiner will be able to compare the identity and characteristics of the deposited biological material with the prior art.

2420 The Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures – the Sequence Rules

Prior to the effective date (October 1, 1990) and implementation of the sequence rules (37 CFR 1.821 through 1.825), applications for patents that included nucleotide or amino acid sequence information posed special problems for the Office. While not related to the disclosure requirements of an invention, problems existed in the presentation, examination and printing of nucleotide and amino acid sequence data that appeared in patent applications because of the lack of uniformity in submission of sequence data to the Office and the impracticality of properly searching and examining sequences submitted in paper form. In summary, the diversity and complexity of nucleotide and amino acid sequence data resulted in searching and analysis difficulties both within the Office and outside the Office, decreased accuracy of search and reproduction and increased costs. These difficulties made the development and implementation of the sequence rules a critical necessity for the Office. As such, the Office amended its regulations to establish a standardized format for descriptions of nucleotide and amino acid sequence data submitted as a part of patent applications, in conjunction with the required submission of that data in computer readable form. The final rules were published in the *Federal Register* at 55 FR 18230 (May 1, 1990) and in the *Official Gazette* at 1114 O.G. 29 (May 15, 1990). The sequence rules went into effect on October 1, 1990. The sequence rules were subsequently revised effective July 1,

1998. See 63 FR 29634 (June 1, 1998) and 1121 O.G. 82 (June 23, 1998)

2421 Overview of the Sequence Rules

2421.01 Applications Affected

The sequence rules require the use of standard symbols and a standard format for sequence data in most sequence-type patent applications. They further require the submission of that data in computer readable form. Compliance is required for most disclosures of sequence data in new applications filed on or after October 1, 1990. The revised sequence rules apply to most new applications filed on or after July 1, 1998. See the final rule publications as cited in MPEP § 2420 for more detailed applicability information.

The Office encourages voluntary compliance for applications not subject to the rules, but all aspects of the rules must be complied with before data will be entered into the database. This includes submission of all statements required by the rules. In exceptional circumstances, it should be noted that the Office may waive the rules via a 37 CFR 1.183 petition.

2421.02 Summary of the Requirements of the Sequence Rules

Basically, the sequence rules define a set of symbols and procedures that are both mandatory and the only way that an applicant is permitted to describe information about a sequence that falls within the definitions used in the rules. Thus, 37 CFR 1.821 defines a sequence for the purpose of the rules, the requirements for specific symbols, formats, paper and computer readable copies of the sequence, and the deadlines for complying with the requirements. 37 CFR 1.822 to 37 CFR 1.824 set forth detailed descriptions of the requirements that are mandatory for the presentation of sequence data, and 37 CFR 1.825 sets forth procedures that are available to an applicant in the event that amendments to the sequence information or replacement of the computer readable copy become necessary.

The sequence rules embrace all unbranched nucleotide sequences with ten or more bases and all unbranched, non-D amino acid sequences with four or more amino acids. The rules apply to all sequences in a given application, whether claimed or not. All such sequences are relevant for the purposes of building a comprehensive database and properly assessing prior art. It is therefore essential that all sequences, whether only disclosed or also claimed, be included in the database.

2421.03 Notification of a Failure to Comply

With respect to the Office's determination of compliance with the sequence rules and the opportunities afforded applicants to satisfy the requirements of the rules, applicants will be notified of easily detectable deficiencies early in the application process. Deficiencies of a more sophisticated nature will likely only be detected by the examiner to whom the application is assigned. Applicants whose computer readable forms are damaged in the mail, are not readable, or are missing mandatory elements will be notified shortly after receipt of the application by the Office. Other errors or inconsistencies will be noted by the examiner early in the examination process. Upon detection of damage or a deficiency, a notice will be sent to the applicant detailing the damage or deficiency and setting at least a 30-day period for reply. The period for reply will usually be 1 month. However, if the notice is sent out with an Office communication having a longer period for reply, the period for reply may be longer than 1 month, e.g., where the notice is sent with an Office action on the merits setting a 3-month period for reply. Extensions of time in which to reply will be available pursuant to 37 CFR 1.136. When an action by the applicant, such as a reply to a Notice to Comply from the Office, is determined to be a *bona fide* attempt to comply with the rules and it is apparent that compliance with some requirement has inadvertently been omitted, the applicant may be given a new time period to correct the omission. See 37 CFR 1.135(c). The relevant form paragraphs and a copy of the Notice to Comply to be used in applications subject to the sequence rules are included in MPEP § 2427 through § 2427.02.

A notification of a failure to comply with the sequence rules will usually be accompanied by an analysis of a submitted computer readable form. Any inquiries regarding a specific computer readable form that has been processed by the Office should be directed to the Systems Branch of the Chemical/Biotechnology Division of the Scientific and Technical Information Center.

2421.04 Future Changes to the Sequence Rules

With general regard to the symbols and format to be used for nucleotide and/or amino acid sequence data set forth in 37 CFR 1.822 and the form and format for se-

quence submissions in computer readable form set forth in 37 CFR 1.824, the Office intends to accommodate progress in the areas of both standardization and computerization as they relate to sequence data by subsequently amending the rules to take into account any such progress. This progress will probably be reflected in the refinement of or liberalization of the rules. For example, progress in the area of the standardization of sequence data will likely result in a more comprehensive rule. For example, the D−amino acids and branched sequences that are currently excluded from the rule may, in the future, be brought within the scope of the rule once the necessary standardization technology becomes available. As a further example, the computer readable form is currently limited to certain forms of electronic media, but it can readily be seen that progress in the technology for developing databases of the type the Office has envisioned will likely permit a broadening of the permissible types of computer readable forms that may be submitted. The same can be said for the computer/operating−system configurations that are currently permitted by the rules. As the Office becomes able to provide greater refinement and liberality in these areas, the Office will do so by the publication of notices in the *Official Gazette* or formal rulemaking proposals, as appropriate.

2422 Nucleotide and/or Amino Acid Sequence Disclosures in Patent Applications

37 CFR 1.821. Nucleotide and/or amino acid sequence disclosures in patent applications.

(a) Nucleotide and/or amino acid sequences as used in §§ 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Branched sequences are specifically excluded from this definition. Sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section. "Specifically defined" means those amino acids other than "Xaa" and those nucleotide bases other than "n" defined in accordance with the World Intellectual Property Organization (WIPO) Handbook on Industrial Property Information and Documentation, Standard ST.25: Standard for the Presentation of Nucleotide and Amino Acid Sequence Listings in Patent Applications (1998), including Tables 1 through 6 in Appendix 2, herein incorporated by reference. (Hereinafter "WIPO Standard ST.25 (1998)"). This incorporation by reference was approved by the Director of the Federal Register in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies of WIPO Standard ST.25 (1998) may be obtained from the World Intellectual Property Organization; 34 chemin des Colombettes; 1211 Geneva 20 Switzerland. Copies of ST.25 may be inspected at the Patent Search Room; Crystal Plaza 3, Lobby Level; 2021 South Clark Place; Arlington, VA 22202. Copies may also be inspected at the Office of the Federal Register, 800 North Capitol Street, NW, Suite 700, Washington, DC. Nucleotides and amino acids are further defined as follows:

(1) *Nucleotides:* Nucleotides are intended to embrace only those nucleotides that can be represented using the symbols set forth in WIPO Standard ST.25 (1998), Appendix 2, Table 1. Modifications, *e.g.*, methylated bases, may be described as set forth in WIPO Standard ST.25 (1998), Appendix 2, Table 2, but shall not be shown explicitly in the nucleotide sequence.

(2) *Amino acids:* Amino acids are those L−amino acids commonly found in naturally occurring proteins and are listed in WIPO Standard ST.25 (1998), Appendix 2, Table 3. Those amino acid sequences containing D−amino acids are not intended to be embraced by this definition. Any amino acid sequence that contains post−translationally modified amino acids may be described as the amino acid sequence that is initially translated using the symbols shown in WIPO Standard ST.25 (1998), Appendix 2, Table 3 with the modified positions; *e.g.*, hydroxylations or glycosylations, being described as set forth in WIPO Standard ST.25 (1998), Appendix 2, Table 4, but these modifications shall not be shown explicitly in the amino acid sequence. Any peptide or protein that can be expressed as a sequence using the symbols in WIPO Standard ST.25 (1998), Appendix 2, Table 3 in conjunction with a description in the Feature section to describe, for example, modified linkages, cross links and end caps, non−peptidyl bonds, etc., is embraced by this definition.

(b) Patent applications which contain disclosures of nucleotide and/or amino acid sequences, in accordance with the definition in paragraph (a) of this section, shall, with regard to the manner in which the nucleotide and/or amino acid sequences are presented and described, conform exclusively to the requirements of §§ 1.821 through 1.825.

(c) Patent applications which contain disclosures of nucleotide and/or amino acid sequences must contain, as a separate part of the disclosure, a paper copy disclosing the nucleotide and/or amino acid sequences and associated information using the symbols and format in accordance with the requirements of §§ 1.822 and 1.823. This paper copy is hereinafter referred to as the "Sequence Listing." Each sequence disclosed must appear separately in the "Sequence Listing." Each sequence set forth in the "Sequence Listing" shall be assigned a separate sequence identifier. The sequence identifiers shall begin with 1 and increase sequentially by integers. If no sequence is present for a sequence identifier, the code "000" shall be used in place of the sequence. The response for the numeric identifier <160> shall include the total number of SEQ ID NOs, whether followed by a sequence or by the code "000."

(d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

(e) A copy of the "Sequence Listing" referred to in paragraph (c) of this section must also be submitted in computer readable form in accordance with the requirements of § 1.824. The computer readable form is a copy of the "Sequence Listing" and will not necessarily be retained as a part of the patent application file. If the computer readable form of a new application is to be identical with the computer readable form of another application of the applicant on file in the Patent and Trademark Office, reference may be made to the other application and computer readable form in lieu of filing a duplicate computer readable form in the new application if the computer readable form in the other application was compliant with all of the requirements of these rules. The new application shall be accompanied by a letter making such reference to the other application and computer readable form, both of which shall

be completely identified. In the new application, applicant must also request the use of the compliant computer readable "Sequence Listing" that is already on file for the other application and must state that the paper copy of the "Sequence Listing" in the new application is identical to the computer readable copy filed for the other application.

(f) In addition to the paper copy required by paragraph (c) of this section and the computer readable form required by paragraph (e) of this section, a statement that the content of the paper and computer readable copies are the same must be submitted with the computer readable form, *e.g.*, a statement that "the information recorded in computer readable form is identical to the written sequence listing."

(g) If any of the requirements of paragraphs (b) through (f) of this section are not satisfied at the time of filing under 35 U.S.C. 111(a) or at the time of entering the national stage under 35 U.S.C. 371, applicant will be notified and given a period of time within which to comply with such requirements in order to prevent abandonment of the application. Any submission in reply to a requirement under this paragraph must be accompanied by a statement that the submission includes no new matter.

(h) If any of the requirements of paragraphs (b) through (f) of this section are not satisfied at the time of filing an international application under the Patent Cooperation Treaty (PCT), which application is to be searched by the United States International Searching Authority or examined by the United States International Preliminary Examining Authority, applicant will be sent a notice necessitating compliance with the requirements within a prescribed time period. Any submission in reply to a requirement under this paragraph must be accompanied by a statement that the submission does not include matter which goes beyond the disclosure in the international application as filed. If applicant fails to timely provide the required computer readable form, the United States International Searching Authority shall search only to the extent that a meaningful search can be performed without the computer readable form and the United States International Preliminary Examining Authority shall examine only to the extent that a meaningful examination can be performed without the computer readable form.

37 CFR 1.821 incorporates by reference the World Intellectual Property Organization (WIPO) Handbook on Industrial Property Information and Documentation, Standard ST.25 (1998), including Tables 1 through 6 of Appendix 2. Copies may be obtained from the World Intellection Property Organization; 34 chemin des Colombettes; 1211 Geneva 20 Switzerland. Copies may be inspected at the Patent Search Room; Crystal Plaza 3, Lobby Level; 2021 South Clark Place; Arlington, VA 22202. Copies may also be inspected at the Office of the Federal Register, 800 North Capitol Street, NW, Suite 700, Washington, DC 20408. These tables are reproduced below.

WIPO Standard ST.25 (1998), Appendix 2, Table 1, provides that the bases of a nucleotide sequence should be represented using the following one−letter code for nucleotide sequence characters:

Table 1: List of Nucleotides

Symbol	Meaning	Origin of designation
a	a	adenine
g	g	guanine
c	c	cytosine
t	t	thymine
u	u	uracil
r	g or a	purine
y	t/u or c	pyrimidine
m	a or c	amino
k	g or t/u	keto
s	g or c	strong interactions 3H−bonds
w	a or t/u	weak interactions 2H−bonds
b	g or c or t/u	not a
d	a or g or t/u	not c
h	a or c or t/u	not g
v	a or g or c	not t, not u
n	a or g or c or t/u, unknown, or other	any

WIPO Standard ST.25 (1998), Appendix 2, Table 2, provides that modified bases may be represented as the corresponding unmodified bases in the sequence itself, if the modified base is one of those listed below and the modification is further described in the Feature section of the Sequence Listing. The codes from the list below may be used in the description (i.e., the specification and drawing, or in the Sequence Listing) but these codes may not be used in the sequence itself.

Table 2: List of Modified Nucleotides

Symbol	Meaning
ac4c	4−acetylcytidine
chm5u	5−(carboxyhydroxymethyl)uridine
cm	2'−O−methylcytidine
cmnm5s2u	5−carboxymethylaminomethyl−2−thiouridine
cmnm5u	5−carboxymethylaminomethyluridine
d	dihydrouridine

fm	2'–O–methylpseudouridine
gal q	beta, D–galactosylqueuosine
gm	2'–O–methylguanosine
i	inosine
i6a	N6–isopentenyladenosine
m1a	1–methyladenosine
m1f	1–methylpseudouridine
m1g	1–methylguanosine
m1i	1–methylinosine
m22g	2,2–dimethylguanosine
m2a	2–methyladenosine
m2g	2–methylguanosine
m3c	3–methylcytidine
m5c	5–methylcytidine
m6a	N6–methyladenosine
m7g	7–methylguanosine
mam5u	5–methylaminomethyluridine
mam5s2u	5–methoxyaminomethyl–2–thiouridine
man q	beta, D–mannosylqueuosine
mcm5s2u	5–methoxycarbonylmethyl–2–thiouridine
mcm5u	5–methoxycarbonylmethyluridine
mo5u	5–methoxyuridine
ms2i6a	2–methylthio–N6–isopentenyladenosine
ms2t6a	N–((9–beta–D–ribofuranosyl–2–methylthiopurine–6–yl)carbamoyl)threonine
mt6a	N–((9–beta–D–ribofuranosylpurine–6–yl)N–methylcarbamoyl)threonine
mv	uridine–5–oxyacetic acid–methylester
o5u	uridine–5–oxyacetic acid
osyw	wybutoxosine
p	pseudouridine
q	queuosine
s2t	5–methyl–2–thiouridine
s2c	2–thiocytidine
s2t	5–methyl–2–thiouridine
s2u	2–thiouridine
s4u	4–thiouridine
t	5–methyluridine
t6a	N–((9–beta–D–ribofuranosylpurine–6–yl)–carbamoyl)threonine
tm	2'–O–methyl–5–methyluridine
um	2'–O–methyluridine
yw	wybutosine
x	3–(3–amino–3–carboxy–propyl)uridine, (acp3)u

WIPO Standard ST.25 (1998), Appendix 2, Table 3, provides that the amino acids should be represented using the following three–letter code with the first letter as a capital.

Table 3: List of Amino Acids

Symbol	Meaning
Ala	Alanine
Cys	Cysteine
Asp	Aspartic Acid
Glu	Glutamic Acid
Phe	Phenylalanine
Gly	Glycine
His	Histidine
Ile	Isoleucine
Lys	Lysine
Leu	Leucine
Met	Methionine
Asn	Asparagine
Pro	Proline
Gln	Glutamine
Arg	Arginine
Ser	Serine
Thr	Threonine
Val	Valine
Trp	Tryptophan
Tyr	Tyrosine

Asx	Asp or Asn
Glx	Glu or Gln
Xaa	unknown or other

WIPO Standard ST.25 (1998), Appendix 2, Table 4, provides that modified and unusual amino acids may be represented as the corresponding unmodified amino acids in the sequence itself if the modified or unusual amino acid is one of those listed below and the modification is further described in the Feature section of the Sequence Listing. The codes from the list below may be used in the description (i.e., the specification and drawings, or in Sequence Listing) but these codes may not be used in the sequence itself.

Table 4: List of Modified and Unusual Amino Acids

Symbol	Meaning
Aad	2–Aminoadipic acid
bAad	3–Aminoadipic acid
bAla	beta–Alanine, beta–Aminopropionic acid
Abu	2–Aminobutyric acid
4Abu	4–Aminobutyric acid, piperidinic acid
Acp	6–Aminocaproic acid
Ahe	2–Aminoheptanoic acid
Aib	2–Aminoisobutyric acid
bAib	3–Aminoisobutyric acid
Apm	2–Aminopimelic acid
Dbu	2,4–Diaminobutyric acid
Des	Desmosine
Dpm	2,2′ –Diaminopimelic acid
Dpr	2,3–Diaminopropionic acid
EtGly	N–Ethylglycine
EtAsn	N–Ethylasparagine
Hyl	Hydroxylysine
aHyl	allo–Hydroxylysine
3Hyp	3–Hydroxyproline
4Hyp	4–Hydroxyproline
Ide	Isodesmosine
aIle	allo–Isoleucine
MeGly	N–Methylglycine, sarcosine
MeIle	N–Methylisoleucine
MeLys	6–N–Methyllysine
MeVal	N–Methylvaline
Nva	Norvaline
Nle	Norleucine
Orn	Ornithine

WIPO Standard ST.25 (1998), Appendix 2, Table 5, provides for feature keys related to DNA sequences.

Table 5: List of Feature Keys Related to Nucleotide Sequences

Key	Description
allele	a related individual or strain contains stable, alternative forms of the same gene which differs from the presented sequence at this location (and perhaps others)
attenuator	(1) region of DNA at which regulation of termination of transcription occurs, which controls the expression of some bacterial operons; (2) sequence segment located between the promoter and the first structural gene that causes partial termination of transcription
C_region	constant region of immunoglobulin light and heavy chains, and T−cell receptor alpha, beta, and gamma chains; includes one or more exons depending on the particular chain
CAAT_signal	CAAT box; part of a conserved sequence located about 75 bp up−stream of the start point of eukaryotic transcription units which may be involved in RNA polymerase binding; consensus=GG (C or T) CAATCT
CDS	coding sequence; sequence of nucleotides that corresponds with the sequence of amino acids in a protein (location includes stop codon); feature includes amino acid conceptual translation
conflict	independent determinations of the "same" sequence differ at this site or region
D−loop	displacement loop; a region within mitochondrial DNA in which a short stretch of RNA is paired with one strand of DNA, displacing the original partner DNA strand in this region; also used to describe the displacement of a region of one strand of duplex DNA by a single stranded invader in the reaction catalyzed by RecA protein
D−segment	diversity segment of immunoglobulin heavy chain, and T−cell receptor beta chain
enhancer	a cis−acting sequence that increases the utilization of (some) eukaryotic promoters, and can function in either orientation and in any location (upstream or downstream) relative to the promoter
exon	region of genome that codes for portion of spliced mRNA; may contain 5'UTR, all CDSs, and 3'UTR
GC_signal	GC box; a conserved GC−rich region located upstream of the start point of eukaryotic transcription units which may occur in multiple copies or in either orientation; consensus=GGGCGG
gene	region of biological interest identified as a gene and for which a name has been assigned
iDNA	intervening DNA; DNA which is eliminated through any of several kinds of recombination
intron	a segment of DNA that is transcribed, but removed from within the transcript by splicing together the sequences (exons) on either side of it
J_segment	joining segment of immunoglobulin light and heavy chains, and T−cell receptor alpha, beta, and gamma chains
LTR	long terminal repeat, a sequence directly repeated at both ends of a defined sequence, of the sort typically found in retroviruses
mat_peptide	mature peptide or protein coding sequence; coding sequence for the mature or final peptide or protein product following post−translational modification; the location does not include the stop codon (unlike the corresponding CDS)

Key	Description
misc_binding	site in nucleic acid which covalently or non−covalently binds another moiety that cannot be described by any other Binding key (primer_bind or protein_bind)
misc_difference	feature sequence is different from that presented in the entry and cannot be described by any other Difference key (conflict, unsure, old_sequence, mutation, variation, allele, or modified_base)
misc_feature	region of biological interest which cannot be described by any other feature key; a new or rare feature
misc_recomb	site of any generalized, site−specific or replicative recombination event where there is a breakage and reunion of duplex DNA that cannot be described by other recombination keys (iDNA and virion) or qualifiers of source key (/insertion_seq, /transposon, /proviral)
misc_RNA	any transcript or RNA product that cannot be defined by other RNA keys (prim_transcript, precursor_RNA, mRNA, 5'clip, 3'clip, 5'UTR, 3'UTR, exon, CDS, sig_peptide, transit_peptide, mat_peptide, intron, polyA_site, rRNA, tRNA, scRNA, and snRNA)
misc_signal	any region containing a signal controlling or altering gene function or expression that cannot be described by other Signal keys (promoter, CAAT_signal, TATA_signal, −35_signal, −10_signal, GC_signal, RBS, polyA_signal, enhancer, attenuator, terminator, and rep_origin)
misc_structure	any secondary or tertiary structure or conformation that cannot be described by other Structure keys (stem_loop and D−loop)
modified_base	the indicated nucleotide is a modified nucleotide and should be substituted for by the indicated molecule (given in the mod_base qualifier value)
mRNA	messenger RNA; includes 5' untranslated region (5'UTR), coding sequences (CDS, exon) and 3' untranslated region (3'UTR)
mutation	a related strain has an abrupt, inheritable change in the sequence at this location
N_region	extra nucleotides inserted between rearranged immunoglobulin segments
old_sequence	the presented sequence revises a previous version of the sequence at this location
polyA_signal	recognition region necessary for endonuclease cleavage of an RNA transcript that is followed by polyadenylation; consensus=AATAAA
polyA_site	site on an RNA transcript to which will be added adenine residues by post−transcriptional polyadenylation
precursor_RNA	any RNA species that is not yet the mature RNA product; may include 5' clipped region (5'clip), 5' untranslated region (5'UTR), coding sequences (CDS, exon), intervening sequences (intron), 3' untranslated region (3'UTR), and 3' clipped region (3'clip)
prim_transcript	primary (initial, unprocessed) transcript; includes 5' clipped region (5'clip), 5' untranslated region (5'UTR), coding sequences (CDS, exon), intervening sequences (intron), 3' untranslated region (3'UTR), and 3' clipped region (3'clip)
primer_bind	non−covalent primer binding site for initiation of replication, transcription, or reverse transcription; includes site(s) for synthetic, for example, PCR primer elements
promoter	region on a DNA molecule involved in RNA polymerase binding to initiate transcription
protein_bind	non−covalent protein binding site on nucleic acid
RBS	ribosome binding site

Key	Description
repeat_region	region of genome containing repeating units
repeat_unit	single repeat element
rep_origin	origin of replication; starting site for duplication of nucleic acid to give two identical copies
rRNA	mature ribosomal RNA; the RNA component of the ribonucleoprotein particle (ribosome) which assembles amino acids into proteins
S_region	switch region of immunoglobulin heavy chains; involved in the rearrangement of heavy chain DNA leading to the expression of a different immunoglobulin class from the same B−cell
satellite	many tandem repeats (identical or related) of a short basic repeating unit; many have a base composition or other property different from the genome average that allows them to be separated from the bulk (main band) genomic DNA
scRNA	small cytoplasmic RNA; any one of several small cytoplasmic RNA molecules present in the cytoplasm and (sometimes) nucleus of a eukaryote
sig_peptide	signal peptide coding sequence; coding sequence for an N−terminal domain of a secreted protein; this domain is involved in attaching nascent polypeptide to the membrane; leader sequence
snRNA	small nuclear RNA; any one of many small RNA species confined to the nucleus; several of the snRNAs are involved in splicing or other RNA processing reactions
source	identifies the biological source of the specified span of the sequence; this key is mandatory; every entry will have, as a minimum, a single source key spanning the entire sequence; more than one source key per sequence is permissable
stem_loop	hairpin; a double−helical region formed by base−pairing between adjacent (inverted) complementary sequences in a single strand of RNA or DNA
STS	Sequence Tagged Site; short, single−copy DNA sequence that characterizes a mapping landmark on the genome and can be detected by PCR; a region of the genome can be mapped by determining the order of a series of STSs
TATA_signal	TATA box; Goldberg−Hogness box; a conserved AT−rich septamer found about 25 bp before the start point of each eukaryotic RNA polymerase II transcript unit which may be involved in positioning the enzyme for correct initiation; consensus=TATA(A or T)A(A or T)
terminator	sequence of DNA located either at the end of the transcript or adjacent to a promoter region that causes RNA polymerase to terminate transcription; may also be site of binding of repressor protein
transit_peptide	transit peptide coding sequence; coding sequence for an N−terminal domain of a nuclear−encoded organellar protein; this domain is involved in post−translational import of the protein into the organelle
tRNA	mature transfer RNA, a small RNA molecule (75−85 bases long) that mediates the translation of a nucleic acid sequence into an amino acid sequence
unsure	author is unsure of exact sequence in this region
V_region	variable region of immunoglobulin light and heavy chains, and T−cell receptor alpha, beta, and gamma chains; codes for the variable amino terminal portion; can be made up from V_segments, D_segments, N_regions, and J_segments
V_segment	variable segment of immunoglobulin light and heavy chains, and T−cell receptor alpha, beta, and gamma chains; codes for most of the variable region (V_region) and the last few amino acids of the leader peptide

Key	Description
variation	a related strain contains stable mutations from the same gene (for example, RFLPs, polymorphisms, etc.) which differ from the presented sequence at this location (and possibly others)
3'clip	3'−most region of a precursor transcript that is clipped off during processing
3'UTR	region at the 3' end of a mature transcript (following the stop codon) that is not translated into a protein
5'clip	5'−most region of a precursor transcript that is clipped off during processing
5'UTR	region at the 5' end of a mature transcript (preceding the initiation codon) that is not translated into a protein
−10_signal	pribnow box; a conserved region about 10 bp upstream of the start point of bacterial transcription units which may be involved in binding RNA polymerase; consensus=TAtAaT
−35_signal	a conserved hexamer about 35 bp upstream of the start point of bacterial transcription units; consensus=TTGACa [ ] or TGTTGACA [ ]

WIPO Standard ST.25 (1998), Appendix 2, Table 6 provides for feature keys related to protein sequences.

Table 6: List of Feature Keys Related to Protein Sequences

Key	Description
CONFLICT	different papers report differing sequences
VARIANT	authors report that sequence variants exist
VARSPLIC	description of sequence variants produced by alternative splicing
MUTAGEN	site which has been experimentally altered
MOD_RES	post−translational modification of a residue
ACETYLATION	N−terminal or other
AMIDATION	generally at the C−terminal of a mature active peptide
BLOCKED	undetermined N− or C−terminal blocking group
FORMYLATION	of the N−terminal methionine
GAMMA−CARBOXYGLUTAMIC ACID HYDROXYLATION	of asparagine, aspartic acid, proline or lysine
METHYLATION	generally of lysine or arginine
PHOSPHORYLATION	of serine, threonine, tyrosine, aspartic acid or histidine
PYRROLIDONE CARBOXYLIC ACID	N−terminal glutamate which has formed an internal cyclic lactam
SULFATATION	generally of tyrosine
LIPID	covalent binding of a lipidic moiety
MYRISTATE	myristate group attached through an amide bond to the N−terminal glycine residue of the mature form of a protein or to an internal lysine residue
PALMITATE	palmitate group attached through a thioether bond to a cysteine residue or through an ester bond to a serine or threonine residue

FARNESYL	farnesyl group attached through a thioether bond to a cysteine residue
GERANYL-GERANYL	geranyl-geranyl group attached through a thioether bond to a cysteine residue
GPI-ANCHOR	glycosyl-phosphatidylinositol (GPI) group linked to the alpha-carboxyl group of the C-terminal residue of the mature form of a protein
N-ACYL DIGLYCERIDE	N-terminal cysteine of the mature form of a prokaryotic lipoprotein with an amide-linked fatty acid and a glyceryl group to which two fatty acids are linked by ester linkages
DISULFID	disulfide bond; the 'FROM' and 'TO' endpoints represent the two residues which are linked by an intra-chain disulfide bond; if the 'FROM' and 'TO' endpoints are identical, the disulfide bond is an interchain one and the description field indicates the nature of the cross-link
THIOLEST	thiolester bond; the 'FROM' and 'TO' endpoints represent the two residues which are linked by the thiolester bond
THIOETH	thioether bond; the 'FROM' and 'TO' endpoints represent the two residues which are linked by the thioether bond
CARBOHYD	glycosylation site; the nature of the carbohydrate (if known) is given in the description field
METAL	binding site for a metal ion; the description field indicates the nature of the metal
BINDING	binding site for any chemical group (co-enzyme, prosthetic group, etc.); the chemical nature of the group is given in the description field
SIGNAL	extent of a signal sequence (prepeptide)
TRANSIT	extent of a transit peptide (mitochondrial, chloroplastic, or for a microbody)
PROPEP	extent of a propeptide
CHAIN	extent of a polypeptide chain in the mature protein
PEPTIDE	extent of a released active peptide
DOMAIN	extent of a domain of interest on the sequence; the nature of that domain is given in the description field
CA_BIND	extent of a calcium-binding region
DNA_BIND	extent of a DNA-binding region
NP_BIND	extent of a nucleotide phosphate binding region; the nature of the nucleotide phosphate is indicated in the description field
TRANSMEM	extent of a transmembrane region
ZN_FING	extent of a zinc finger region
SIMILAR	extent of a similarity with another protein sequence; precise information, relative to that sequence is given in the description field
REPEAT	extent of an internal sequence repetition
HELIX	secondary structure: Helices, for example, Alpha-helix, 3(10) helix, or Pi-helix

STRAND	secondary structure: Beta−strand, for example, Hydrogen bonded beta−strand, or Residue in an isolated beta−bridge
TURN	secondary structure: Turns, for example, H−bonded turn (3−turn, 4−turn, or 5−turn)
ACT_SITE	amino acid(s) involved in the activity of an enzyme
SITE	any other interesting site on the sequence
INIT_MET	the sequence is known to start with an initiator methionine
NON_TER	the residue at an extremity of the sequence is not the terminal residue; if applied to position 1, this signifies that the first position is not the N−terminus of the complete molecule; if applied to the last position, it signifies that this position is not the C−terminus of the complete molecule; there is no description field for this key
NON_CONS	non consecutive residues; indicates that two residues in a sequence are not consecutive and that there are a number of unsequenced residues between them
UNSURE	uncertainties in the sequence; used to describe region(s) of a sequence for which the authors are unsure about the sequence assignment

FILING INTERNATIONALLY

The revisions to 37 CFR 1.821 through 1.825 are the result of an effort to harmonize the PTO, PCT, EPO and JPO Sequence Listing requirements to the extent possible. The requirements of WIPO Standard ST.25 are substantially identical to the requirements of 37 CFR 1.821 through 1.825. PatentIn Version 2.0 software, now available (see MPEP § 2430), meets all of the requirements of WIPO Standard ST.25 (1998). The requirements of 37 CFR 1.821 through 1.825, however, are less stringent than the requirements of WIPO Standard ST.25 (1998). Thus, applicants who wish to file in countries which adhere to WIPO Standard ST.25 (1998) should consider the following when not using PatentIn Version 2.0:

(A) The WIPO Standard ST.25 (1998) does not permit submissions using a Macintosh computer;

(B) The WIPO Standard ST.25 (1998) does not accept the range of media permitted by 37 CFR 1.821 through 1.825;

(C) The answers in fields <221> and <222> must use selections from Tables 5 and 6 of WIPO Standard ST.25 (1998) to comply with that standard. The terms from these Tables are considered language neutral vocabulary;

(D) Any free text in numeric identifier <223> of a Sequence Listing will not be translated and thus must also appear in the specification of applications filed under WIPO Standard ST.25 (1998) for compliance;

(E) A CRF filed after the filing of an application under the PCT does not form part of the disclosure and will not be published in the pamphlet;

(F) Paragraph 39 of WIPO Standard ST.25 (1998) requires the specific wording "the information recorded on the form is identical to the written sequence listing"; and

(G) WIPO Standard ST.25 (1998), paragraph 24, requires spaces between specified numeric identifiers in the Sequence Listing.

2422.01 Definitions of Nucleotide and/or Amino Acids for Purpose of Sequence Rules

37 CFR 1.821(a) presents a definition for "nucleotide and/or amino acid sequences." This definition sets forth limits, in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten

or more nucleotides. Branched sequences are specifically excluded from this definition. Sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section. "Specifically defined" means those amino acids other than "Xaa" and those nucleotide bases other than "n" defined in accordance with the World Intellectual Property Organization (WIPO) Handbook on Industrial Property Information and Documentation, Standard ST.25: Standard for the Presentation of Nucleotide and Amino Acid Sequence Listings in Patent Applications (1998), including Tables 1 through 6 in Appendix 2 (see MPEP § 2422).

The limit of four or more amino acids was established for consistency with limits in place for industry database collections whereas the limit of ten or more nucleotides, while lower than certain industry database limits, was established to encompass those nucleotide sequences to which the smallest probe will bind in a stable manner. The limits for amino acids and nucleotides are also consistent with those established for sequence data exchange with the Japanese Patent Office and the European Patent Office.

37 CFR 1.821(a)(1) and 37 CFR 1.821(a)(2) present further definitions for those nucleotide and amino acid sequences that are intended to be embraced by the sequence rules. Situations in which the applicability of the rules are in issue will be resolved on a case-by-case basis.

Nucleotide sequences are further limited to those that can be represented by the symbols set forth in 37 CFR 1.822(b), which incorporates by reference WIPO Standard ST.25 (1998), Appendix 2, Table 1 (see MPEP § 2422). The presence of other than typical 5′ to 3′ phosphodiester linkages in a nucleotide sequence does not render the rules inapplicable. The Office does not want to exclude linkages of the type commonly found in naturally occurring nucleotides, e.g., eukaryotic end capped sequences.

Amino acid sequences are further limited to those listed in 37 CFR 1.822(b), which incorporates by reference WIPO Standard ST.25 (1998), Appendix 2, Table 3 (see MPEP § 2422), and those L-amino acids that are commonly found in naturally occurring proteins. The limitation to L-amino acids is based upon the fact that there currently exists no widely accepted standard nomenclature for representing the scope of amino acids encompassed by non-L-amino acids, and, as such, the process of meaningfully encoding these other amino acids for computerized searching and printing is not currently feasible. The presence of one or more D-amino acids in a sequence will exclude that sequence from the scope of the rules. (Voluntary compliance is, however, encouraged in these situations; the symbol "Xaa" can be used to represent D-amino acids.) The sequence rules embrace "[a]ny peptide or protein that can be expressed as a sequence using the symbols in WIPO Standard ST.25 (1998), Appendix 2, Table 3 in conjunction with a description in the Feature section to describe, for example, modified linkages, cross links and end caps, non-peptidyl bonds, etc." 37 CFR 1.821(a)(2).

With regard to amino acid sequences, the use of the terms "peptide or protein" implies, however, that the amino acids in a given sequence are linked by at least three consecutive peptide bonds. Accordingly, an amino acid sequence is not excluded from the scope of the rules merely due to the presence of a single non-peptidyl bond. If an amino acid sequence can be represented by a string of amino acid abbreviations, with reference, where necessary, to a features table to explain modifications in the sequence, the sequence comes within the scope of the rules. However, the rules are not intended to encompass the subject matter that is generally referred to as synthetic resins.

2422.02 The Requirement for Exclusive Conformance; Sequences Presented in Drawing Figures

37 CFR 1.821(b) requires exclusive conformance, with regard to the manner in which the nucleotide and/or amino acid sequences are presented and described, with the sequence rules for all applications that include nucleotide and amino acid sequences that fall within the definitions. This requirement is necessary to minimize any confusion that could result if more than one format for representing sequence data was employed in a given application. It is also expected that the required standard format will be more readily and widely accepted and adopted if its use is exclusive, as well as mandatory.

In view of the fact that many significant sequence characteristics may only be demonstrated by a figure, the exclusive conformance requirement of this section may be relaxed for drawing figures. This is especially true in view of the fact that the representation of double stranded nucleotides is not permitted in the "Sequence Listing" and many significant nucleotide features, such

as "sticky ends" and the like, will only be shown effectively by reference to a drawing figure. Further, the similarity or homology between/among sequences can only be depicted in an effective manner in a drawing figure. Similarly, drawing figures are recommended for use with amino acid sequences to depict structural features of the corresponding protein, such as finger regions and Kringle regions. The situations discussed herein are given by way of example only and there may be many other reasons for relaxing the requirements of this section for the drawing figures. It should be noted, though, that when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings.

2422.03 The Requirements for a Sequence Listing and Sequence Identifiers; Sequences Embedded in Application Text; Variants of a Presented Sequence

37 CFR 1.821(c) requires that applications containing nucleotide and/or amino acid sequences that fall within the above definitions, contain, as a separate part of the disclosure on paper copy, a disclosure of the nucleotide and/or amino acid sequences, and associated information, using the format and symbols that are set forth in 37 CFR 1.822 and 37 CFR 1.823. This separate part of the disclosure, beginning on a new page within the specification, is referred to as the "Sequence Listing," and requires that each sequence disclosed in the application appear separately in the "Sequence Listing," with each sequence further being assigned a sequence identification number, referred to as "SEQ ID NO." A plurality of sequences may, if feasible, be presented on a single page, and this may be extended to the separate presentation of both nucleotide and amino acid sequences on the same page. The requirement for sequence identification numbers, at a minimum, requires that each sequence be assigned a different number for purposes of identification. However, where practical and for ease of reference, sequences should be presented in the separate part of the application in numerical order and in the order in which they are discussed in the application.

The requirement for compliance in 37 CFR 1.821(c) is directed to "disclosures of nucleotide and/or amino acid sequences." (Emphasis added.) All sequence information, whether claimed or not, that meets the length thresholds in 37 CFR 1.821(a) is subject to the rules. The goal of the Office is to build a comprehensive database that can be used for, inter alia, the purpose of assessing the prior art. It is therefore essential that all sequence information, whether only disclosed or also claimed, be included in the database. In those instances in which prior art sequences are only referred to in a given application by name and a publication or accession reference, they need not be included as part of the "Sequence Listing," unless an examiner considers the referred– to sequence to be "essential material," per MPEP § 608.01(p). However, if the applicant presents the sequence as a string of particular bases or amino acids, it is necessary to include the sequence in the "Sequence Listing," regardless of whether the applicant considers the sequence to be prior art. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing."

It is generally acceptable to present a single, general sequence in accordance with the sequence rules and to discuss and/or claim variants of that general sequence without presenting each variant as a separate sequence in the "Sequence Listing." By way of example only, the following types of sequence disclosures would be treated as noted herein by the Office. With respect to "conservatively modified variants thereof" of a sequence, the sequences may be described as SEQ ID NO:X and "conservatively modified variants thereof," if desired. With respect to a sequence that "may be deleted at the C–terminus by 1, 2, 3, 4, or 5 residues," all of the implied variations do not need to be included in the "Sequence Listing." If such a situation were encompassed by the rules, it would introduce far too much complexity into the "Sequence Listing" and the Office's database. The possible mathematical variations that could result from this type of language could reasonably require a "Sequence Listing" that would be thousands of pages in length. In this latter example, only the undeleted sequence needs to be included in the "Sequence Listing," and the sequences may be described as SEQ ID NO:X from which deletions have been made at the C–terminus by 1, 2, 3, 4, or 5 resi-

dues. The Office's database will only contain the undeleted sequence.

37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application. This requirement is also intended to permit references, in both the description and claims, to sequences set forth in the "Sequence Listing" by the use of assigned sequence identifiers without repeating the sequence in the text of the description or claims. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in the "Sequence Listing." Where a sequence is embedded in the text of an application, it must be presented in a manner that complies with the requirements of the sequence rules.

The rules do not alter, in any way, the requirements of 35 U.S.C. 112. The implementation of the rules has had no effect on disclosure and/or claiming requirements. The rules, in general, or the use of sequence identifiers throughout the specification and claims, specifically, should not raise any issues under 35 U.S.C. 112, first or second paragraphs. The use of sequence identification numbers (SEQ ID NO:X) only provides a shorthand way for applicants to discuss and claim their inventions. These identification numbers do not in any way restrict the manner in which an invention can be claimed.

2422.04 The Requirement for a Computer Readable Copy of the Official Paper Copy of the Sequence Listing

37 CFR 1.821(e) requires the submission of a copy of the "Sequence Listing" in computer readable form. The information on the computer readable form will be entered into the Office's database for searching and printing nucleotide and amino acid sequences. This electronic database will also enable the Office to exchange patented sequence data, in electronic form, with the Japanese Patent Office and the European Patent Office. It should be noted that the Office's database complies with the confidentiality requirement imposed by 35 U.S.C. 122. Pending application sequences are maintained in the database separately from published or patented sequences. That is, the Office will not exchange or make public any information on any sequence until the patent application containing that information is published or matures into a patent, or as otherwise allowed by 35 U.S.C. 122.

The second sentence of 37 CFR 1.821(e) indicates that, as between the paper copy of the "Sequence Listing" and the computer readable copy thereof, the paper copy serves as the official copy. However, the Office may permit correction of the paper copy, at the least, during the pendency of a given application by reference to the computer readable copy thereof if both the paper and computer readable forms were submitted at the time of filing of the application and the totality of the circumstances otherwise substantiate the proposed correction. A mere discrepancy between the paper copy and the computer readable form may not, in and of itself, be sufficient to justify a proposed correction. In this regard, the Office will assume that the computer readable form has been incorporated by reference into the application when the paper and computer readable forms were submitted at the time of filing of the application. The Office will attempt to accommodate or address all correction issues, but it must be kept in mind that the real burden rests with the applicant to ensure that any discrepancies between the paper copy and the computer readable form are eliminated or minimized. Applicants should be aware that there will be instances where the applicant may have to suffer the consequences of any discrepancies between the two. The paper copy also serves as the official copy for priority purposes. The Office does not desire to be bound by a requirement to permanently preserve computer readable forms for support, priority or correction purposes. For example, the Office will make corrections, where appropriate, by reference to the computer readable form as long as the computer readable form is still available to the Office. However, once use of the computer readable form by the Office for processing has ended, i.e., once the Office has entered the data contained on the computer readable form into the appropriate database, the Office does not intend to further preserve the computer readable form submitted by the applicant.

2422.05 Reference to Previously Filed Identical Computer Readable Form; Continuing or Derivative Applications; Request for Transfer of Computer Readable Form

The last three sentences of 37 CFR 1.821(e) set forth the procedure to be followed when a computer readable form of a given application is identical with a computer readable form of another application. In that situation, an applicant may make reference to the other application and computer readable form therein in lieu of filing a duplicate computer readable form in the given application. That is, additional computer readable forms will not be required in derivative or continuing applications if the sequence information is exactly the same, i.e., with no additions or deletions, as that in a parent or previously filed application in which a complying computer readable form had been filed. If sequence information is deleted from or added to that submitted in a previously filed application, the procedure in this paragraph is not available and a new computer readable form is required. To take advantage of the procedure outlined in this section, applicants must request that the previously submitted sequence information be used in the given application in much the same manner as applicants must now request the transfer of drawings in derivative or continuing applications. A letter must be submitted in the given application requesting use of the previously filed sequence information. The letter must completely identify the other application, by application number, and the computer readable form, by indicating whether it was the only computer readable form filed in that application or whether it was the second, or subsequent, computer readable form filed.

A sample letter requesting transfer of the previously filed sequence information is set forth below:

> The paper copy of the Sequence Listing in this application [application number], is identical to the computer readable copy of the Sequence Listing filed in application [application number], filed [date]. In accordance with 37 CFR 1.821(e), please use the [first–filed, last–filed or only, whichever is applicable] computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the instant application. A paper copy of the Sequence Listing is [included in the originally–filed specification of the instant application, included in a separately filed preliminary amendment for incorporation into the specification, whichever is applicable].

2422.06 Requirement for Statement Regarding Content of Paper and Computer Readable Copies of Sequence Listing

37 CFR 1.821(f) requires that the paper and computer readable copies of the "Sequence Listing" be accompanied by a statement that the content of the paper and computer readable copies are the same, at the time when the computer readable form is submitted. Such a statement may be made by the applicant. See MPEP § 2428 for further information and Sample Statements.

2422.07 Requirements for Compliance, Statements Regarding New Matter, and Sanctions for Failure to Comply

37 CFR 1.821(g) requires compliance with the requirements of 37 CFR 1.821(b) through (f), as discussed above, if they are not satisfied at the time of filing under 35 U.S.C. 111(a) or at the time of entering the national stage of an international application under 35 U.S.C. 371, within the period of time set in a notice requiring compliance. Failure to comply will result in the abandonment of the application. Submissions in reply to requirements under this paragraph must be accompanied by a statement that the submission includes no new matter. Such a statement may be made by the applicant. Extensions of time in which to reply to a requirement under this paragraph are available pursuant to 37 CFR 1.136. When an action by the applicant is a *bona fide* attempt to comply with these rules and it is apparent that compliance with some requirement has inadvertently been omitted, the applicant may be given a new time period to correct the omission. See 37 CFR 1.135(c).

Applications filed under 35 U.S.C. 111(b) need not comply with 37 CFR 1.821 through 1.825, however, applicants are encouraged to file a Sequence Listing as defined in 37 CFR 1.821(c) for ease of identification of the sequence information contained in the provisional application.

37 CFR 1.821(h) requires compliance with the requirements of 37 CFR 1.821(b) through (f), as discussed

above, within the time period prescribed in a notice requiring compliance in an international application filed in the United States Receiving Office under the Patent Cooperation Treaty (PCT), if the above noted requirements are not satisfied at the time of filing. Submissions in reply to requirements under this paragraph must be accompanied by a statement that the submission does not include matter which goes beyond the disclosure in the international application as filed. Such a statement may be made by an applicant. International applications that fail to comply with any of the requirements of 37 CFR 1.821(b)–(f) will be searched to the extent possible without the benefit of the information in computer readable form.

The requirement to submit a statement that a submission in reply to the requirements of this section does not include new matter or matter which goes beyond the disclosure in the application as filed is not the first instance in which the applicant has been required to ensure that there is not new matter upon amendment. The requirement is analogous to that found in 37 CFR 1.125 regarding substitute specifications. When a substitute specification is required because the number or nature of amendments would make it difficult to examine the application, the applicant must include a statement that the substitute specification includes no new matter. The necessity of requiring a substitute "Sequence Listing," or pages thereof, is similar to the necessity of requiring a substitute specification and, likewise, the burden is on the applicant to ensure that no new matter is added. Applicants have a duty to comply with the statutory prohibition (35 U.S.C. 132 and 35 U.S.C. 251) against the introduction of new matter.

It should be noted that the treatment accorded errors in sequencing or any other errors prior to the implementation date of the sequence rules will be no different for those applications filed on or after the implementation date of these rules. The correction of errors in sequencing or any other errors that are made in describing an invention are, as they have always been, subject to the statutory prohibition (35 U.S.C. 132 and 35 U.S.C. 251) against the introduction of new matter.

2422.08 Presumptions Regarding Compliance

Neither the presence nor absence of information which is not required under the sequence rules will create a presumption that such information is necessary to satisfy any of the requirements of 35 U.S.C. 112. Further, the grant of a patent on an application that is subject to 37 CFR 1.821 through 37 CFR 1.825 constitutes a conclusive presumption that the granted patent complies with the requirements of these rules.

2422.09 Box Sequence; Hand Delivery of Sequence Listings and Computer Readable Forms

To facilitate administrative processing of all papers associated with sequence rule compliance, all computer readable forms, fees, and papers accompanying them filed in the Office should be marked "Box SEQUENCE."

Correspondence relating to the sequence rules may also be hand–delivered to the Group. In cases of hand delivery to the Customer Service Window or to the Group, the floppy disk or tape should be placed in a protective mailer labeled with at least the application number, if available. The labeling requirements of 37 CFR 1.824(a)(6) must also be complied with. The use of staples and clips, if any, should be confined to carefully attaching the mailer to the submitted papers without contact or compression of the magnetic media which may cause the disk or tape to be unreadable. In no situations should additional or complimentary copies of diskettes or tapes be delivered to examiners or other Office personnel.

2423 Symbols and Format To Be Used for Nucleotide and/or Amino Acid Sequence Data

37 CFR 1.822. Symbols and format to be used for nucleotide and/or amino acid sequence data.

(a) The symbols and format to be used for nucleotide and/or amino acid sequence data shall conform to the requirements of paragraphs (b) through (e) of this section.

(b) The code for representing the nucleotide and/or amino acid sequence characters shall conform to the code set forth in the tables in WIPO Standard ST.25 (1998), Appendix 2, Tables 1 and 3. This incorporation by reference was approved by the Director of the Federal Register in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies of ST.25 may be obtained from the World Intellectual Property Organization; 34 chemin des Colombettes; 1211 Geneva 20 Switzerland. Copies of ST.25 may be inspected at the Patent Search Room; Crystal Plaza 3, Lobby Level; 2021 South Clark Place; Arlington, VA 22202. Copies may also be inspected at the Office of the Federal Register, 800 North Capitol Street, NW, Suite 700, Washington, DC. No code other than that specified in these sections shall be used in nucleotide and amino acid sequences. A modified base or modified or unusual amino acid may be presented in a given sequence as the corresponding unmodified base or

amino acid if the modified base or modified or unusual amino acid is one of those listed in WIPO Standard ST.25 (1998), Appendix 2, Tables 2 and 4, and the modification is also set forth in the Feature section. Otherwise, each occurrence of a base or amino acid not appearing in WIPO Standard ST.25 (1998), Appendix 2, Tables 1 and 3, shall be listed in a given sequence as "n" or "Xaa," respectively, with further information, as appropriate, given in the Feature section, preferably by including one or more feature keys listed in WIPO Standard ST.25 (1998), Appendix 2, Tables 5 and 6.

(c) *Format representation of nucleotides.* (1) A nucleotide sequence shall be listed using the lower-case letter for representing the one-letter code for the nucleotide bases set forth in WIPO Standard ST.25 (1998), Appendix 2, Table 1.

(2) The bases in a nucleotide sequence (including introns) shall be listed in groups of 10 bases except in the coding parts of the sequence. Leftover bases, fewer than 10 in number, at the end of noncoding parts of a sequence shall be grouped together and separated from adjacent groups of 10 or 3 bases by a space.

(3) The bases in the coding parts of a nucleotide sequence shall be listed as triplets (codons). The amino acids corresponding to the codons in the coding parts of a nucleotide sequence shall be typed immediately below the corresponding codons. Where a codon spans an intron, the amino acid symbol shall be typed below the portion of the codon containing two nucleotides.

(4) A nucleotide sequence shall be listed with a maximum of 16 codons or 60 bases per line, with a space provided between each codon or group of 10 bases.

(5) A nucleotide sequence shall be presented, only by a single strand, in the 5 to 3 direction, from left to right.

(6) The enumeration of nucleotide bases shall start at the first base of the sequence with number 1. The enumeration shall be continuous through the whole sequence in the direction 5 to 3. The enumeration shall be marked in the right margin, next to the line containing the one-letter codes for the bases, and giving the number of the last base of that line.

(7) For those nucleotide sequences that are circular in configuration, the enumeration method set forth in paragraph (c)(6) of this section remains applicable with the exception that the designation of the first base of the nucleotide sequence may be made at the option of the applicant.

(d) *Representation of amino acids.* (1) The amino acids in a protein or peptide sequence shall be listed using the three-letter abbreviation with the first letter as an upper case character, as in WIPO Standard ST.25 (1998), Appendix 2, Table 3.

(2) A protein or peptide sequence shall be listed with a maximum of 16 amino acids per line, with a space provided between each amino acid.

(3) An amino acid sequence shall be presented in the amino to carboxy direction, from left to right, and the amino and carboxy groups shall not be presented in the sequence.

(4) The enumeration of amino acids may start at the first amino acid of the first mature protein, with the number 1. When presented, the amino acids preceding the mature protein, *e.g.*, pre-sequences, pro-sequences, pre-pro-sequences and signal sequences, shall have negative numbers, counting backwards starting with the amino acid next to number 1. Otherwise, the enumeration of amino acids shall start at the first amino acid at the amino terminal as number 1. It shall be marked below the sequence every 5 amino acids. The enumeration method for amino acid sequences that is set forth in this section remains applicable for amino acid sequences that are circular in configuration, with the exception that the designation of the first amino acid of the sequence may be made at the option of the applicant.

(5) An amino acid sequence that contains internal terminator symbols (*e.g.*, "Ter", "*", or ".", etc.) may not be represented as a single amino acid sequence, but shall be presented as separate amino acid sequences.

(e) A sequence with a gap or gaps shall be presented as a plurality of separate sequences, with separate sequence identifiers, with the number of separate sequences being equal in number to the number of continuous strings of sequence data. A sequence that is made up of one or more noncontiguous segments of a larger sequence or segments from different sequences shall be presented as a separate sequence.

Tables 1-6 of WIPO Standard ST.25 (1998), Appendix 2, are reproduced in MPEP § 2422.

2423.01 Format and Symbols To Be Used in Sequence Listings

37 CFR 1.822 sets forth the format and symbols to be used for listing nucleotide and/or amino acid sequence data. The codes for representing the nucleotide and/or amino acid characters in the sequences are set forth in the tables of WIPO Standard ST.25 (1998), Appendix 2, Tables 1 and 3. See MPEP § 2422. No other symbols shall be used in nucleotide and amino acid sequences. The "modified base" and "modified and unusual amino acid" codes appearing in WIPO Standard ST.25 (1998), Appendix 2, Tables 2 and 4 (see 37 CFR 1.822 and MPEP § 2422) are not to be used in setting forth the sequences, but, they may be used in the description and/or the "Sequence Listing" corresponding to, but not including, the sequence itself. A modified base or amino acid may be presented in a given sequence as the corresponding unmodified base or amino acid if the modified base or amino acid is one of those listed in WIPO Standard ST.25 (1998), Appendix 2, Table 2 or 4 and the modification is also set forth in the features section of the Sequence Listing. Otherwise, all bases or amino acids not appearing in WIPO Standard ST.25 (1998), Appendix 2, Table 1 or 3 must be listed in a given sequence as "n" or "Xaa," respectively, with further information given in the features section of the "Sequence Listing." See 37 CFR 1.823(b).

In 37 CFR 1.822(b) and 37 CFR 1.822(d), the use of three-letter codes for amino acids is required. The use of the three-letter codes for amino acids is preferred over the one-letter codes from the perspective of facilitating the examiner's review of the application papers, including the "Sequence Listing", and the public's, as well as the examiner's, use of the printed patents. The three-letter codes must be presented using the upper

case for the first character and lower case for the remaining two characters.

37 CFR 1.822(c) through (e) set forth the format for presenting sequence data. These paragraphs set forth the manner in which the characters in sequences are to be grouped, spaced, presented and numbered.

2423.02 Depiction of Coding Regions

If applicant chooses to depict coding regions, 37 CFR 1.822 (c)(3) requires the amino acids corresponding to the codons in the coding parts of a nucleotide sequence to be typed immediately below the corresponding codons. Further, in 37 CFR 1.822 (c)(3), the situation in which a codon spans an intron has been addressed. In those situations, the "amino acid symbol shall be typed below the portion of the codon containing two nucleotides." This requirement clarifies the representation of an amino acid that corresponds to a codon that spans an intron.

It should be noted that the sequence rules do not, in any way, require the depiction of coding regions or the amino acids corresponding to the codons in those coding regions. 37 CFR 1.822 (d) only requires that where amino acids corresponding to the codons in the coding parts of a nucleotide sequence are depicted, they must be depicted below the corresponding codons. There is absolutely no requirement in the rules to depict coding regions. Nor is there a requirement to separately list the amino acids corresponding to the codons in the coding parts of a nucleotide sequence unless the applicant desires to discuss the amino acids as a separate sequence. That is, when the coding parts of a nucleotide sequence and their corresponding amino acids have been identified, if applicant desires to discuss those amino acids in the coding parts of the nucleotide as a separate sequence, those amino acids must also be set forth as a separate sequence. The separate submission of the amino acid sequence that corresponds to the coding parts of a nucleotide sequence is, however, recommended and encouraged because the amino acid sequence may not be captured in the sequence database if it is only presented in the "Sequence Listing" as a mixed nucleotide and amino acid sequence.

2423.03 Presentation and Enumeration of Sequences

37 CFR 1.822(c)(5) provides that nucleotide sequences shall only be represented by a single strand, in the 5′ to 3′ direction, from left to right. That is, double stranded nucleotides shall not be represented in the "Sequence Listing." A double stranded nucleotide may be represented as two single stranded nucleotides, and any relationship between the two may be shown in the drawings.

The procedures for presenting and numbering amino acid sequences are set forth in 37 CFR 1.822(d). Two alternatives are presented for numbering amino acid sequences. Amino acid sequences may be numbered with respect to the identification of the first amino acid of the first mature protein or with respect to the first amino acid appearing at the amino terminal. The enumeration procedure for nucleotides is set forth in 37 CFR 1.822(c)(6). Sequences that are circular in configuration are intended to be encompassed by these rules, and numbering procedures for them are provided in 37 CFR 1.822(c)(7) and (d)(4). The numbering procedures set forth in 37 CFR 1.822(c) and (d) are not necessarily intended to be consistent with all currently employed numbering procedures. The objective here is to establish a reasonable numbering procedure that can readily be followed and adhered to. These formatting procedures also reflect those that have been agreed to for electronic data exchange with the JPO and the EPO.

In 37 CFR 1.822(e) the procedures for presenting and numbering hybrid and gapped sequences are set forth. A sequence that is made up of one or more noncontiguous segments of a larger sequence or segments from different sequences, i.e., a hybrid sequence, shall be presented as a separate sequence. A "gap" for the purpose of this section is not intended to embrace a gap or gaps that is/are introduced into the presentation of otherwise continuous sequence information in, e.g., a drawing figure, to show alignments or similarities with other sequences. The "gaps" referred to in this section are gaps representing unknown or undisclosed regions in a sequence between regions that are known or disclosed. In the situation where a contiguous fragment of a sequence that has already been properly set forth in a "Sequence Listing" is discussed and/or claimed, the fragment does not need to be separately included in the "Sequence Listing." It may be referred to in the specification, claims or drawings as,

e.g., "residues 2 through 33 of SEQ ID NO:12," assuming that SEQ ID NO:12 has been properly included in the "Sequence Listing."

2424 Requirements for Nucleotide and/or Amino Acid Sequences as Part of the Application Papers

37 CFR 1.823. Requirements for nucleotide and/or amino acid sequences as part of the application papers.

(a) The "Sequence Listing" required by § 1.821(c), setting forth the nucleotide and/or amino acid sequences and associated information in accordance with paragraph (b) of this section, must begin on a new page and must be titled "Sequence Listing". The "Sequence Listing" preferably should be numbered independently of the numbering of the remainder of the application. Each page of the "Sequence Listing" should contain no more than 66 lines and each line should contain no more than 72 characters. A fixed-width font should be used exclusively throughout the "Sequence Listing."

(b) The "Sequence Listing" shall, except as otherwise indicated, include the actual nucleotide and/or amino acid sequence, the numeric identifiers and their accompanying information as shown in the following table. The numeric identifier shall be used only in the "Sequence Listing." The order and presentation of the items of information in the "Sequence Listing" shall conform to the arrangement given below. Each item of information shall begin on a new line and shall begin with the numeric identifier enclosed in angle brackets as shown. The submission of those items of information designated with an "M" is mandatory. The submission of those items of information designated with an "O" is optional. Numeric identifiers <110> through <170> shall only be set forth at the beginning of the "Sequence Listing." The following table illustrates the numeric identifiers.

Numeric Identifier	Definition	Comments and format	Mandatory (M) or Optional (O)
<110>	Applicant.....	Preferably max. of 10 names; one name per line; preferable format: Surname, Other Names and/or Initials.	M.
<120>	Title of Invention.....	.....	M.
<130>	File Reference.....	Personal file reference.....	M when filed prior to assignment or appl. number
<140>	Current Application Number.	Specify as: US 07/999,999 or PCT/US96/99999.	M, if available.
<141>	Current Filing Date.....	Specify as: yyyy-mm-dd.....	M, if available.
<150>	Prior Application Number.	Specify as: US 07/999,999 or PCT/US96/99999.	M, if applicable include priority documents under 35 USC 119 and 120
<151>	Prior Application Filing Date.	Specify as: yyyy-mm-dd	M, if applicable
<160>	Number of SEQ ID NOs.	Count includes total number of SEQ ID NOs.....	M.
<170>	Software.....	Name of software used to create the Sequence Listing.	O.
<210>	SEQ ID NO:#:.....	Response shall be an integer representing the SEQ ID NO shown.	M.
<211>	Length.....	Respond with an integer expressing the number of bases or amino acid residues.	M.
<212>	Type.....	Whether presented sequence molecule is DNA, RNA, or PRT (protein). If a nucleotide sequence contains both DNA and RNA fragments, the type shall be "DNA." In addition, the combined DNA/RNA molecule shall be further described in the <220> to <223> feature section.	M.
<213>	Organism.....	Scientific name, i.e. Genus/ species, Unknown or Artificial Sequence. In addition, the "Unknown" or "Artificial Sequence" organisms shall be further described in the <220> to <223> feature section.	M.

<220>	Feature.....	Leave blank after <220>. <221–223> provide for a description of points of biological significance in the sequence..	M, under the following conditions: if "n," "Xaa," or a modified or unusual L–amino acid or modified base was used in a sequence; if ORGANISM is "Artificial Sequence" or "Unknown'; if molecule is combined DNA/RNA"
<221>	Name/Key.....	Provide appropriate identifier for feature, preferably from WIPO Standard ST.25 (1998), Appendix 2, Tables 5 and 6.	M, under the following conditions: if "n," "Xaa," or a modified or unusual L–amino acid or modified base was used in a sequence.
<222>	Location.....	Specify location within sequence; where appropriate state number of first and last bases/amino acids in feature.	M, under the following conditions: if "n," "Xaa," or a modified or unusual L–amino acid or modified base was used in a sequence.
<223>	Other Information.....	Other relevant information; four lines maximum.....	M, under the following conditions: if "n," "Xaa," or a modified or unusual L–amino acid or modified base was used in a sequence; if ORGANISM is "Artificial Sequence" or "Unknown"; if molecule is combined DNA/RNA.
<300>....	PublicationInformation....	Leave blank after <300>	O.
<301>	Authors.....	Preferably max of ten named authors of publication; specify one name per line; preferable format: Surname, Other Names and/or Initials.	O.
<302>	Title.....	.....	O.
<303>	Journal.....	.....	O.
<304>	Volume.....	.....	O.
<305>	Issue	.....	O.
<306>	Pages	.....	O.
<307>	Date.....	Journal date on which data published; specify as yyyy– mm–dd, MMM–yyyy or Season– yyyy.	O.
<308>	Database Accession Number.	Accession number assigned by database including database name.	O.
<309>	Database Entry Date.....	Date of entry in database; specify as yyyy–mm–dd or MMM–yyyy.	O.
<310>	Patent Document Number.	Document number; for patent– type citations only. Specify as, for example, US 07/999,999.	O.
<311>	Patent Filing Date.....	Document filing date, for patent–type citations only; specify as yyyy–mm–dd.	O.
<312>	Publication Date.....	Document publication date, for patent–type citations only; specify as yyyy–mm–dd.	O.
<313>	Relevant Residues.....	FROM (position) TO (position).....	O.
<400>	Sequence.....	SEQ ID NO should follow the numeric identifier and should appear on the line preceding the actual sequence.	M.

2424.01 Informational Requirements for the Sequence Listing

37 CFR 1.823 sets forth the informational requirements for inclusion in the separate part of the disclosure on paper copy (the "Sequence Listing") that must be submitted in accordance with 37 CFR 1.821(c). This section lists the items of information that are to be included in the "Sequence Listing," which constitutes the separate part of the disclosure on paper copy. The items of information are to be presented in the "Sequence Listing" in the order in which those items are listed in 37 CFR 1.823. Page and line length requirements are set forth. The requirement to use a fixed width font to present sequence data is also set forth. This latter requirement is made to ensure that the desired sequence character spacing and numbering is maintained upon printing. The numeric identifier for each item of information shall not include the explanatory information included in 37 CFR 1.823.

2424.02 Sequence Listing Numeric Identifiers

37 CFR 1.823(b) sets forth the order and presentation of the items of information in the Sequence Listing. Each item of information in the Sequence Listing must include the appropriate numeric identifier and its accompanying information as shown in the table below. Each item of information must begin on a new line with the numeric identifier enclosed in angle brackets. The submission of those items of information designated with an "M" is mandatory. The submission of those items of information designated with an "O" is optional. Numeric identifiers <110> through <170> must be set forth at the beginning of the Sequence Listing.

The following table illustrates the numeric identifiers. See MPEP § 2431 for a sample Sequence Listing.

Numeric Identifier	Definition	Comments and format	Mandatory (M) or Optional (O)
<110>	Applicant.....	Preferably max. of 10 names; one name per line; preferable format: Surname, Other Names and/or Initials.	M.
<120>	Title of Invention.....	.....	M.
<130>	File Reference.....	Personal file reference.....	M when filed prior to assignment or appl. number
<140>	Current Application Number.	Specify as: US 07/999,999 or PCT/US96/99999.	M, if available.
<141>	Current Filing Date.....	Specify as: yyyy−mm−dd.....	M, if available.
<150>	Prior Application Number.	Specify as: US 07/999,999 or PCT/US96/99999.	M, if applicable include priority documents under 35 USC 119 and 120
<151>	Prior Application Filing Date.	Specify as: yyyy−mm−dd	M, if applicable
<160>	Number of SEQ ID NOs.	Count includes total number of SEQ ID NOs.....	M.
<170>	Software.....	Name of software used to create the Sequence Listing.	O.
<210>	SEQ ID NO:#:.....	Response shall be an integer representing the SEQ ID NO shown.	M.
<211>	Length.....	Respond with an integer expressing the number of bases or amino acid residues.	M.
<212>	Type.....	Whether presented sequence molecule is DNA, RNA, or PRT (protein). If a nucleotide sequence contains both DNA and RNA fragments, the type shall be "DNA." In addition, the combined DNA/RNA molecule shall be further described in the <220> to <223> feature section.	M.
<213>	Organism.....	Scientific name, i.e. Genus/species, Unknown or Artificial Sequence. In addition, the "Unknown" or "Artificial Sequence" organisms shall be further described in the <220> to <223> feature section.	M.
<220>	Feature.....	Leave blank after <220>. <221−223> provide for a description of points of biological significance in the sequence..	M, under the following conditions: if "n," "Xaa," or a modified or unusual L−amino acid or modified base was used in a sequence; if ORGANISM is "Artificial Sequence" or "Unknown'; if molecule is combined DNA/RNA"
<221>	Name/Key.....	Provide appropriate identifier for feature, preferably from WIPO Standard ST.25 (1998), Appendix 2, Tables 5 and 6.	M, under the following conditions: if "n," "Xaa," or a modified or unusual L−amino acid or modified base was used in a sequence.
<222>	Location.....	Specify location within sequence; where appropriate state number of first and last bases/amino acids in feature.	M, under the following conditions: if "n," "Xaa," or a modified or unusual L−amino acid or modified base was used in a sequence.

<223>	Other Information.....	Other relevant information; four lines maximum.....	M, under the following conditions: if "n," "Xaa," or a modified or unusual L–amino acid or modified base was used in a sequence; if ORGANISM is "Artificial Sequence" or "Unknown"; if molecule is combined DNA/RNA.
<300>....	PublicationInformation....	Leave blank after <300>	O.
<301>	Authors.....	Preferably max of ten named authors of publication; specify one name per line; preferable format: Surname, Other Names and/or Initials.	O.
<302>	Title.....	.....	O.
<303>	Journal.....	.....	O.
<304>	Volume.....	.....	O.
<305>	Issue	.....	O.
<306>	Pages	.....	O.
<307>	Date.....	Journal date on which data published; specify as yyyy– mm–dd, MMM–yyyy or Season– yyyy.	O.
<308>	Database Accession Number.	Accession number assigned by database including database name.	O.
<309>	Database Entry Date.....	Date of entry in database; specify as yyyy–mm–dd or MMM–yyyy.	O.
<310>	Patent Document Number.	Document number; for patent– type citations only. Specify as, for example, US 07/999,999.	O.
<311>	Patent Filing Date.....	Document filing date, for patent–type citations only; specify as yyyy–mm–dd.	O.
<312>	Publication Date.....	Document publication date, for patent–type citations only; specify as yyyy–mm–dd.	O.
<313>	Relevant Residues.....	FROM (position) TO (position)	O.
<400>	Sequence.....	SEQ ID NO should follow the numeric identifier and should appear on the line preceding the actual sequence.	M.

2424.03 Additional Miscellaneous Requirements

Throughout 37 CFR 1.823(b), the items of information relating to patent applications and patent publications should be provided keeping in mind the appropriate standards that have been established by the World Intellectual Property Organization (WIPO). In general, an application should be identified by a country code, a number and a filing date, while a published patent document should be identified by a country code, a number and kind code. Proper citation of priority patent applications is covered in MPEP § 201.14(d). For published patent documents, the country code, number and kind code will appear on the front page of the document. Unpublished PCT applications are identified by the letters PCT, the country code of the Receiving Office, the last two digits of the year of filing and a number, e.g., PCT/AT81/00033, PCT/FR88/00100. A published PCT application is identified by the letters WO, the last two digits of the year of publication, a number and a kind code, e.g., WO82/02827A, WO88/06811A. Country codes from WIPO Standard ST.3 Annex A and kind codes from WIPO Standard ST.16 are reproduced in MPEP § 1851. Questions on proper citation of patent documents should be directed to the Search and Information Resources Administration, International Liaison Staff.

In 37 CFR 1.823(b), numeric identifier <110>, the item of information relating to "APPLICANT" should be limited to a maximum of the first ten named applicants in the application. Similarly, in numeric identifier <301>, the item of information relating to "AUTHORS" should be limited to to a maximum of the first ten named authors in the publication.

In 37 CFR 1.823(b) "yyyy−mm−dd" is the format for the presentation of patent related date information in the "Sequence Listing." Other date information may also be presented as MMM−yyyy or Season−yyyy. The lower case letters designate numeric responses and the upper case letters designate alphabetical responses. As such, March 2, 1988, would be presented as 1988−03−02 or MAR 1988.

In numeric identifiers <220> − <223>, relating to "Features" or the description of the points of biological significance in a given sequence, it is recommended, but not required, that the information that is provided by the applicant conform to the controlled vocabulary that is set forth in GenBank's "Feature Representation in Nucleotide Sequence Data Libraries," Release 57.0, as may be amended. Further, the feature "LOCATION" should be specified using the syntax of the DDBJ/EMBL/GenBank Feature Table Definition. See MPEP § 2422 when filing in countries which adhere to WIPO Standard ST.25.

In numeric identifiers <300> − <312>, publication information for a given sequence is collected. The publication information encompasses both patent−type publications and non−patent literature publications. Numeric identifier <313>, Relevant Residues, is intended to collect information relating to the correspondence between a sequence set forth in the "Sequence Listing" and published sequence information. The starting (FROM) and end (TO) positions in the listed sequence that correspond to the published sequence information should be set forth.

2425 Form and Format for Nucleotide and/or Amino Acid Sequence Submissions in Computer Readable Form

37 CFR 1.824. Form and format for nucleotide and/or amino acid sequence submissions in computer readable form.

(a) The computer readable form required by § 1.821(e) shall meet the following specifications:

(1) The computer readable form shall contain a single "Sequence Listing" as either a diskette, series of diskettes, or other permissible media outlined in paragraph (c) of this section.

(2) The "Sequence Listing" in paragraph (a) (l) of this section shall be submitted in American Standard Code for Information Interchange (ASCII) text. No other formats shall be allowed.

(3) The computer readable form may be created by any means, such as word processors, nucleotide/amino acid sequence editors or other custom computer programs; however, it shall conform to all specifications detailed in this section.

(4) File compression is acceptable when using diskette media, so long as the compressed file is in a self−extracting format that will decompress on one of the systems described in paragraph (b) of this section.

(5) Page numbering shall not appear within the computer readable form version of the "Sequence Listing" file.

(6) All computer readable forms shall have a label permanently affixed thereto on which has been hand−printed or typed: the name of the applicant, the title of the invention, the date on which the data were recorded on the computer readable form, the operating system used, a reference number, and an application serial number and filing date, if known.

(b) Computer readable form submissions must meet these format requirements:

(1) Computer: IBM PC/XT/AT, or compatibles, or Apple Macintosh;

(2) Operating System: MS−DOS, Unix or Macintosh;

(3) Line Terminator: ASCII Carriage Return plus ASCII Line Feed;

(4) Pagination: Continuous file (no "hard page break" codes permitted);

(c) Computer readable form files submitted may be in any of the following media:

(1) Diskette: 3.50 inch, 1.44 Mb storage; 3.50 inch, 720 Kb storage; 5.25 inch, 1.2 Mb storage; 5.25 inch, 360 Kb storage.

(2) Magnetic tape: 0.5 inch, up to 24000 feet; Density: 1600 or 6250 bits per inch, 9 track; Format: Unix tar command; specify blocking factor (not "block size"); Line Terminator: ASCII Carriage Return plus ASCII Line Feed.

(3) 8mm Data Cartridge: Format: Unix tar command; specify blocking factor (not "block size"); Line Terminator: ASCII Carriage Return plus ASCII Line Feed.

(4) CD−ROM: Format: ISO 9660 or High Sierra Format

(5) Magneto Optical Disk: Size/Storage Specifications: 5.25 inch, 640 Mb.

(d) Computer readable forms that are submitted to the Office will not be returned to the applicant.

37 CFR 1.824 sets forth the requirements for sequence submissions in computer readable form. Any computer operating system may be utilized to produce a sequence submission, provided that the system is capable of producing a file having the characteristics specified in 37 CFR 1.824, and is capable of writing the properly formatted file to one of the acceptable electronic media. If a given sequence and its associated information cannot practically or possibly fit on the electronic media required in 37 CFR 1.824(c), an exception via a non−fee petition to waive this provision will normally be

granted. As set forth in 37 CFR 1.824(d), the computer readable forms that are submitted in accordance with these rules will not be returned to the applicant. 37 CFR 1.824(a)(6) requires the labeling, with appropriate identifying information, of the computer readable forms that are submitted in accordance with these rules.

2426 Amendments to or Replacement of Sequence Listing and Computer Readable Copy Thereof

37 CFR 1.825. Amendments to or replacement of sequence listing and computer readable copy thereof.

(a) Any amendment to the paper copy of the "Sequence Listing" (§ 1.821(c)) must be made by the submission of substitute sheets. Amendments must be accompanied by a statement that indicates support for the amendment in the application, as filed, and a statement that the substitute sheets include no new matter.

(b) Any amendment to the paper copy of the "Sequence Listing," in accordance with paragraph (a) of this section, must be accompanied by a substitute copy of the computer readable form (§ 1.821(e)) including all previously submitted data with the amendment incorporated therein, accompanied by a statement that the copy in computer readable form is the same as the substitute copy of the "Sequence Listing."

(c) Any appropriate amendments to the "Sequence Listing" in a patent; *e.g.*, by reason of reissue or certificate of correction, must comply with the requirements of paragraphs (a) and (b) of this section.

(d) If, upon receipt, the computer readable form is found to be damaged or unreadable, applicant must provide, within such time as set by the Commissioner, a substitute copy of the data in computer readable form accompanied by a statement that the substitute data is identical to that originally filed.

37 CFR 1.825 sets forth the procedures for amending the "Sequence Listing" and the computer readable copy thereof. The procedures that have been defined in 37 CFR 1.825 involve the submission of either substitute sheets of the "Sequence Listing" or substitute copies of the computer readable form, in conjunction with statements that indicate support for the amendment in the application, as filed, and that the substitute sheets or copies include no new matter. (See MPEP § 2428 for further information and Sample Statements.) The requirement for statements regarding the absence of new matter follows current practice relating to the submission of substitute specifications, as set forth in 37 CFR 1.125. 37 CFR 1.825 (c) addresses the situation where amendments to the "Sequence Listing" are made after a patent has been granted, e.g., by a certificate of correction, reissue or reexamination. 37 CFR 1.825 (d) addresses the possibility and presents a remedy for the situation where the computer readable form may be found by the Office to be damaged or unreadable.

2427 Form Paragraphs and Notice to Comply

2427.01 Form Paragraphs

In order to minimize the extension of pendency due to the implementation of the sequence rules, all compliance issues should be addressed in a single communication with the applicant. That communication should set a 1-month (not less than 30 days) period for reply that may be extended in accordance with the provisions of 37 CFR 1.136. However, depending upon the nature of applicant's reply, a follow-up communication regarding the sequence rules may be necessary. The form paragraphs that follow are to be used in these communications. The form paragraphs should be used as follows:

7.200 – This form paragraph should be used for the first mailing of a Notice to Comply.

7.201 – This form paragraph should be used for the first mailing of a CRF Diskette Problem Report.

7.202 – This form paragraph should be used when an applicant has made a *bona fide* attempt to comply but the reply generates an error listing from the Scientific and Technical Information Center (STIC). This should be used for a second mailing to applicant unless it is evident that there has been a deliberate omission; this form paragraph may also be used to extend the period for reply for the initially mailed notice.

7.203 – This form paragraph should be used when there has been a deliberate omission in the reply or where the reason the reply is incomplete cannot be characterized as an apparent oversight or instance of inadvertence.

¶ *7.200 Cover Letter for Use With Notice To Comply With Sequence Rules*

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 – 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Examiner Note:

1. Use this form paragraph **only for the initial communication to the applicant.** Use either 7.203 or 7.203 for subsequent communications.
2. Conclude action with appropriate form paragraph(s) 7.100–7.102.
3. Print this paragraph on a PTOL–90 and attach a Notice To Comply With Requirements for Patent Applications Containing Nucleotide And/Or Amino Acid Sequence Disclosures, along with a marked–up copy of the Raw Sequence Listing, if any.

¶ *7.201 Cover Letter for Use with CRF Diskette Problem Report*

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). A computer readable form (CRF) of the sequence listing was submitted. However, the CRF could not be processed by the Scientific and Technical Information Center (STIC) for the reason(s) set forth on the attached CRF Diskette Problem Report.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 – 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached CRF Diskette Problem Report with the reply.

Examiner Note:

1. Use this form paragraph **only for the initial communication to the applicant.** Use either 7.203 or 7.203 for subsequent communications.
2. Conclude action with appropriate form paragraph(s) 7.100–7.102.
3. Print this paragraph on a PTOL–90 and attach the CRF Diskette Problem Report.

¶ *7.202 CRF Submission Is Not Fully Responsive, Bona Fide Attempt*

The reply filed **[1]** is not fully responsive to the Office communication mailed **[2]** for the reason(s) set forth on the attached Notice To Comply With The Sequence Rules or CRF Diskette Problem Report.

Since the above–mentioned reply appears to be *bona fide*, applicant is given a TIME PERIOD of **ONE (1) MONTH** or **THIRTY (30) DAYS** from the mailing date of this notice, whichever is longer, within which to supply the omission or correction in order to avoid abandonment. EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136(a).

Examiner Note:

1. This form paragraph may be used whether or not the six–month period for reply has expired. It is intended for use whenever a **bona fide** reply has been submitted. This practice does not apply where there has been a deliberate omission of some necessary part of a complete reply or where the reason the reply is incomplete cannot be characterized as an apparent oversight or apparent inadvertence. Under such cases the examiner has no authority to grant an extension if the six–month period for reply has expired. Use form paragraph 7.203 under such circumstances.
2. In bracket 1, insert the date of the reply and in bracket 2, insert the mail date of the communication requiring compliance.
3. Print this paragraph on a PTOL–90 and attach a Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures, along with a marked–up copy of the Raw Sequence Listing, or CRF Diskette Problem Report.
4. See 37 CFR 1.135(c), 1.821(g); MPEP §§ 710.02(c), 711.02(a), 714.02 and 714.03.

¶ *7.203 CRF Submission Is Not Fully Responsive*

The communication filed **[1]** is not fully responsive to the communication mailed **[2]** for the reason(s) set forth on the attached Notice To Comply With The Sequence Rules or CRF Diskette Problem Report.

If a complete reply has not been submitted by the time the shortened statutory period set in the communication mailed **[3]** has expired, this application will become abandoned unless applicant corrects the deficiency and obtains an extension of time under 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period.

Examiner Note:

1. This form paragraph may not be used when the six month period for reply has expired. Use this form paragraph in the situation where, in the reply (within the six–months), there has been a deliberate omission of some necessary part of a complete reply. When the reply appears to be bona fide, but through an apparent oversight or inadvertence failed to provide a complete reply, use form paragraph 7.202.
2. In bracket 1, insert the date of the reply and in brackets 2 and 3, insert the mail date of the communication requiring compliance.
3. Print this paragraph on a PTOL–90 and attach a Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures, along with a marked–up copy of the Raw Sequence Listing, or CRF Diskette Problem Report.

2427.02 Notice To Comply

The text of the Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence and for Amino Acid Sequence Disclosures, Form PTO–1661, follows. The appropriate box on the notice should be checked depending upon the particular deficiencies that have been identified. A copy of the "Raw Sequence Listing," where available, should also be sent to the applicant. The "Raw Sequence Listing" should also be entered into the application file upon receipt from STIC.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE

DATE MAILED:

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821–1.825 for the following reason(s):

☐ 1. This application fails to comply with the requirements of 37 CFR 1.821–1.825.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. The content of the computer readable form, however, does not comply with the requirements of 37 CFR 1.822 and/or 1.832, as indicated on the attached marked–up copy of the "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7. OTHER:_____

_____

APPLICANT MUST PROVIDE:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing."

☐ An initial or substitute paper copy of the "Sequence Listing," as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b) or 1.825(d).

FOR QUESTIONS REGARDING COMPLIANCE WITH THESE REQUIREMENTS, PLEASE CONTACT:

☐ For Rules Interpretation, call (703) 308–1123.

☐ For CRF submission help, call (703) 308–4212.

☐ For PatentIn software help, call (703) 308–6856.

_____

Customer Service Center
Initial Patent Examination Division (703) 308–1202

FORM**PTO–1661**(Rev. 7/97) **PART 1 – ATTORNEY/APPLICANT COPY**

2428 Sample Statements

Sample language for the statements required to support sequence rule submissions is provided below. These statements are given by way of example only; other language may, of course, be used. For the statements that relate to the assertion that the content of the paper and computer readable copies are the "same," it is acknowledged that there may be some nonsubstantive differences between the two, e.g., page numbers and page breaks may be present in the paper copy but not in the computer readable copy thereof. This requirement for sameness relates to the informational content of the paper and computer readable copies relevant to the requirements of the sequence rules.

37 CFR 1.821(f) – I hereby state that the information recorded in computer readable form is identical to the written sequence listing.

37 CFR 1.821(g) [or (h)] – I hereby state that the submission, filed in accordance with 37 CFR 1.821(g) [or (h)], herein does not include new matter [or matter which goes beyond the disclosure in the international application].

37 CFR 1.825(a) – I hereby state that the amendments, made in accordance with 37 CFR 1.825(a), included in the substitute sheet(s) of the Sequence Listing are supported in the application, as filed, at _____. I hereby state that the substitute sheet(s) of the Sequence Listing does (do) not include new matter.

37 CFR 1.825(b) – I hereby state that the substitute copy of the computer readable form, submitted in accordance with 37 CFR 1.825(b), is the same as the amended Sequence Listing.

37 CFR 1.825(d) – I hereby state that the substitute copy of the computer readable form, submitted in accordance with 37 CFR 1.825(d), is identical to that originally filed.

2429 Helpful Hints for Compliance

The Office has now had a good deal of experience in the implementation of the sequence rules. The following list sets forth helpful hints, for both examiners and applicants, for compliance. For the most part, the list is a compilation of frequently asked questions.

—Compliance is not a filing date issue.

—Compliance is not a 35 U.S.C. 112 issue.

—Compliance is not a 35 U.S.C. 119/120 issue.

—Compliance is not a new matter issue. The standard for resolution of inconsistencies between the paper and the electronic copies and/or errors in the paper copy of sequence information is based on the new matter standard.

—Compliance can be achieved via amendment.

—The paper copy of Sequence Listing is an integral part of the application. The Sequence Listing must begin on a new page, should appear at the end of the application, and preferably should be numbered independently of the numbering of the remainder of the application. The new page that begins the "Sequence Listing" should be entitled "Sequence Listing." If not submitted as such at filing, the Sequence Listing must be inserted into the application via amendment, e.g., by preliminary amendment.

—Substitute pages must be used for changes to the Sequence Listing.

—Angle brackets and numeric identifiers listed in 37 CFR 1.823 are very important for our database. Extra punctuation should not be used in Sequence Listings.

—The computer readable form cannot contain page numbers. Page numbers should only be placed on the paper copy of the Sequence Listing.

—The PatentIn computer program is not the only means by which to comply with the rules. Any word processing program can be used to generate a Sequence Listing if it has the capability to convert a file into ASCII text.

—If a word processing program is used to generate a "Sequence Listing," hard page break controls should not be used and margins should be adjusted to the smallest setting.

—Word processing files should not be submitted to the Office; the Sequence Listing generated by a word processing file should be saved as an ASCII text file for submission. Most word processing programs provide this feature.

—Statements in accordance with 37 CFR 1.821(f), (g), (h) and 37 CFR 1.825 and proper labeling in accordance with 37 CFR 1.824(a)(6) should be noted. Sample statements to support filings and submissions in accordance with 37 CFR 1.821 through 1.825 are provided in MPEP § 2428 Sample Statements.

—Use Box Sequence.

—Three and a half inch disks are less fragile than five and a quarter inch disks.

—On nucleotide sequences, since only single strands may be depicted in the "Sequence Listing," show strands in 5′ to 3′ direction.

—The single stranded nucleotide depicted in the "Sequence Listing" may represent a strand of a nucleotide sequence that may be single or double

stranded which may be, further, linear or circular. An amino acid sequence or peptide may be linear or circular. In some instances, a sequence may be both single stranded and double stranded and/or both linear and circular. The response "not relevant" is also an acceptable response for both "Strandedness" and "Topology."

—Numeric identifiers "<140>, Current Application Number," "<141>, Current Filing Date," "<150>, Prior Application Number," and "<151>, Prior Application Filing Date," should appear in the "Sequence Listing" in all cases. If the information about the current application is not known or is unavailable at the time of completing the Sequence Listing, then the lines following numeric identifiers <140> and <141> should be left blank. This would normally be the case when the "Sequence Listing" is included in a newly filed application. Similarly, if information regarding prior applications is inapplicable, or not known at the time of completing the "Sequence Listing" but will be later filed, then the numeric identifiers <150> and <151> should appear with the line following the numeric identifiers left blank.

—If you receive a Notice to Comply that should not have been sent to you, send a letter in the form of a request for reconsideration of the notice to the organization sending the notice.

—There are a limited number of mandatory items of information. They are identifed in MPEP § 2424.02 Sequence Listing Numeric Identifiers.

—Figures can be used to convey information not readily conveyed by the Sequence Listing. The exclusive conformance requirement of 37 CFR 1.821(b) will be relaxed for drawing figures. However, the sequence information so conveyed must still be included in a "Sequence Listing" and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the "Brief Description of the Drawings."

—Extra copies of computer readable forms should not be sent to examiners.

—Inosine may be represented by the use of "I" in the features section, otherwise use "n."

—Stop codons, represented by an asterisk, are not permitted in amino acid sequences.

—Punctuation should not be used in a sequence to indicate unknown nucleotide bases or amino acid residues nor should punctuation be used to delimit active or functional regions of a sequence. These regions should be noted as Features of the sequence per 37 CFR 1.823(b) (see numeric identifiers <220> – <223>.

—The presence of an unnatural amino acid in a sequence does not have the same effect as the presence of a D–amino acid. The sequence may still be subject to the rules even though one or more of the amino acids is not naturally occurring.

—Cyclic and branched peptides are causing some confusion in the application of the rules. Specific questions should be directed to Group 1650 personnel.

—A cyclic peptide with a tail is regarded as a branched sequence, and thereby exempt from the rules, if all bonds adjacent to the amino acid from which the tail emanates are normal peptide bonds.

—Sequences that have variable–length regions depicted as, for example, Ala Ala Leu Leu $(Xaa\ Xaa)_n$ Ile Pro where n=0–234 or $agccttgggaca(nnnnn)_mgtcatt$ where m=0–354 or Ser Met Ala Xaa Ser where Xaa could be 1, 2, 3, 4 and/or 5 amino acids must still comply with the Sequence Rules. The method to use is to repeat the variable–length region as many times as the maximum length and specify in the Features section that the amino acid (or nucleotide) at a specified position is either absent or present. The variables Xaa and n may stand for only one residue, hence the need to repeat the variable. The correct way to submit the third example is Ser Met Ala Xaa Xaa Xaa Xaa Xaa Ser combined with an explanation in the Features section of the listing that any one or all of amino acids 4–8 can either be present or absent.

—Single letter amino acid abbreviations are not acceptable within the Sequence Listing but may appear elsewhere in the application.

—Zero (0) is not used when the numbering of amino acids uses negative numbers to distinguish the mature protein.

—Subscripts or superscripts are not permitted in a Sequence Listing.

—If a "Sequence Listing" is amended, an entirely new computer readable form is required regardless of the triviality of the amendment. Amendments to the paper copy of the "Sequence Listing" must be made by substitute sheets.

—Note field length limitations. For specific instances, they may be waived, but compliance is encouraged.

—The exclusive conformance requirement of 37 CFR 1.821(b) requires that any amendment of the

sequence information in a "Sequence Listing" be accompanied by an amendment to the corresponding information, if any, embedded in the text of the specification or presented in a drawing figure.

—Any inquiries regarding a specific computer readable form that has been processed by the Office should be directed to the Systems Branch of the Chemical/Biotechnology Division of the Scientific and Technical Information Center.

2430 PatentIn Information; Utilities Programs; Training

In those areas of biotechnology in which nucleotide and/or amino acid sequence information is significant, many patent applicants are accustomed to, or familiar with, the submission of such sequence information, in electronic form, to various sequence databases, such as GenBank, which is produced by the National Institutes of Health. In order to facilitate such submissions, or merely for the purpose of researching and developing sequence information, many eventual patent applicants also generate or encode sequence information in computer readable form. In order to further facilitate compliance with the sequence rules, the Office has made available to the public an input program that is based on the AuthorIn program produced by GenBank. This input program, called PatentIn version 1.3, was specifically tailored to the requirements of the sequence rules which were in effect prior to July 1, 1998.

The Office has completed an updated version of the PatentIn program, called PatentIn version 2.0. This new version is compliant with Microsoft Windows 3.1x, 95, and NT. This new version also incorporates changes in the required format for the Sequence Listing to ensure compliance with the new World Intellectual Property Office (WIPO) Standard ST.25 which became effective July 1, 1998 and with revisions to the U.S. sequence rules which became effective July 1, 1998. This new WIPO Standard simplifies the Sequence Listing requirements, and harmonizes the format among all Trilateral Patent Offices and many other patent offices around the world. By using PatentIn version 2.0, customers will be able to generate a Sequence Listing once and use that same listing to file at multiple patent offices worldwide. Applications filed in the U.S. after July 1, 1998 containing Sequence Listings prepared using PatentIn version 1.3 will not be in compliance with the U.S. sequence rules. Applications filed in the member countries of WIPO after July 1, 1998 containing Sequence Listings prepared using PatentIn version 1.3 will not be in compliance with ST.25.

The new PatentIn version 2.0, and the companion User Manual, are available on the Office world wide web site (www.uspto.gov) for free downloading. Copies of both the program and the user manual are also available on 3 1/2 inch floppy diskette at a cost of $25.00 for each item. PatentIn version 2.0 has similar space, memory, and system requirements as those for PatentIn version 1.3, except that to function properly PatentIn 2.0 requires a Microsoft Windows operating system. See MPEP § 1730 for additional information regarding ordering and using PatentIn.

While use of the PatentIn program is not required for compliance with the sequence rules, its use is highly recommended as Office experience has shown that submissions developed with PatentIn are far less likely to include errors than those developed without the program. The many automatic features of the PatentIn program also greatly ease the generation of Sequence Listings when compared to generating them by hand in a word processing environment. This is especially true for Sequence Listings that include many sequences and/or sequences having great lengths.

The Office provides hands–on training in the use of the PatentIn and associated utilities programs. The classes are held in Washington D.C. as demand warrants. In addition, on site training may be arranged at locations outside Washington, D.C. To express interest in such classes, please contact the Search and Information Resources Administration.

2431 Sample Sequence Listing

A sample "Sequence Listing" is included below.

SAMPLE SEQUENCE LISTING

```
<110> Smith, John
      Smith, Jane

<120> Example of a Sequence Listing

<130> 01-00001

<140> US 08/999,999

<141> 1998-02-28

<150> EP 91000000
<151> 1997-12-31

<160> 2

<170> PatentIn ver. 2.0

<210> 1
<211> 403
<212> DNA
<213> Paramecium aurelia

<220>
<221> CDS
<222> 341..394

<300>
<301> Doe, Richard
<302> Isolation and Characterization of a Gene Encoding a
      Protease from Paramecium sp.
<303> Journal of Fictional Genes
<304> 1
<305> 4
<306> 1 - 7
<307> 1988-06-20

<400> 1
ctactctact ctactctcat ctactatctt ctttggatct ctgagtctgc ctgagtggta      60

ctcttgagtc ctggagatct ctcctctcac atgtgatcgt cgagactgac cgatagatcg      120

ctgactgact ctgagatagt cgagcccgta cgagacccgt cgagggtgac agagagtggg      180

cgcgtgcgcg cagagcgccg cgccggtgcg cgcgcgagtg cgcggtgggc cgcgcgaggg      240

ctttcgcggc agcggcggcg ctttccggcg cgcgcccgtc cgcccctaga cctgagaggt      300

cttctcttcc ctcctcttca ctagagaggt ctatatatac atg gtt tca atg ttc        355
                                              Met Val Ser Met Phe
                                              1               5
```

```
agc ttg tct ttc aaa tgg cct gga ttt tgt ttg ttt gtt tgtttgctc     403
Ser Leu Ser Phe Lys Trp Pro Gly Phe Cys Leu Phe Val
                  10                  15

<210> 2
<211> 18
<212> PRT
<213> Paramecium aurelia

<400> 2

Met Val Ser Met Phe Ser Leu Ser Phe Lys Trp Pro Gly Phe Cys Leu
1               5                   10                  15

Phe Val
```

2434 Examination of Patent Applications Claiming Large Numbers of Nucleotide Sequences

The Patent and Trademark Office recently published its policy for the examination of patent applications that claim large numbers of nucleotide sequences in the *Official Gazette*, 1192 O.G. 68 (November 19, 1996). Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141. In establishing the new policy, the Commissioner has partially waived the requirements of 37 CFR 1.141 and will permit a reasonable number of such nucleotide sequences to be claimed in a single application.

Under this policy, in most cases, up to 10 independent and distinct nucleotide sequences will be examined in a single application without restriction. Those sequences which are patentably indistinct from the sequences selected by the applicant will also be examined. Nucleotide sequences encoding the same protein are not considered to be independent and distinct and will continue to be examined together. In some exceptional cases, the complex nature of the claimed material may necessitate that the reasonable number of sequences to be selected be less than 10. In other cases, applicants may petition pursuant to 37 CFR 1.181 for examination of additional nucleotide sequences by providing evidence that the different nucleotide sequences do not cover independent and distinct inventions. For examples of typical nucleotide sequence claims and additional information on the search and examination procedures, see the above cited O.G. Notice. See also MPEP § 803.04.

●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●