BRAZIL

Guidelines for Examining Patent Applications in the Field of Biotechnology

Entry into Force : March 12, 2015

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1 Requirements for protection in biotechnology

The requirements of novelty and inventive step are discussed in the Guidelines for Examining Patent Applications. Only a few specificities of biotechnology patent applications will be highlighted in this Appendix.

1.1 Industrial application

The concept of industrial application in the field of biotechnology must comply with that set forth in the Guidelines for Examining Patent Applications (Block II), and due regard shall be given to the definition of a utility for the invention claimed.

When the invention involves biological sequences, the requirement of industrial application is only met when a utility is disclosed for said sequence.

Accordingly, if a patent application identifies a new sequence by homology, and the homologous sequence described in the state of the art has a known function, a new sequence identified in the patent application is susceptible to industrial application provided that this utility is identified in the specification.

Example 1:

The protein of SEQ ID NO: 1 was identified in different patients with prostate cancer, and no biological function for this protein is known in the state of the art. It is noted that this protein described in the application is an important marker for diagnosing prostate cancer.

The inventions related to this protein (for example, use, composition, diagnosis kit) are susceptible to industrial application since the application clearly discloses a practical use for this sequence (marker for diagnosing in vitro prostate cancer), even if its biological function is still unknown.

Example 2:

The application discloses a protein of SEQ ID NO: 1 which was isolated from yeasts; however, it discloses no function/application for the same and it presents no homology with any protein having a known function.

The specification discloses a merely speculative list of applications with no technical basis capable of supporting any practical application for the protein. This protein and/or its use and/or compositions comprising same are not susceptible to industrial application, since said subject matters present no defined practical utility.

2 Conditions for protection

2.1 Unity of invention

The patent application shall refer to a single invention or to a group of interrelated inventions so as to comprise a single general concept (Art. 22 of the Industrial Property Law 9,279/96 - LPI; see Guidelines for Examining Patent Applications, Block I).

Example 3: Multiple nucleic acid molecules that share a common structure and encode proteins with common properties.

Claim 1: Modified nucleic acid characterized by being selected from SEQ ID NO: 1, 2, or 3.

The specification mentions that the three nucleic acids encode dehydrogenases that include a sequence of conserved motive defining the catalytic site. The three nucleic acids are isolated from three different sources (mouse, rat and human) and modified. The specification clearly shows that these three nucleic acids are homologous based on their global sequence identity (85-95% identity) for both sequences of nucleotides and amino acids.

The same technical characteristics or equivalents that are shared among the nucleic acid molecules lies in their common properties (encoding dehydrogenases) and their shared structural elements are essential for the common property (the conserved motive). So, there is a special technical characteristic and SEQ ID NOs: 1, 2, and 3 have unity of invention.

2.2 Full disclosure (Art. 24)

Article 24 of LPI determines that the specification must clearly and sufficiently describe the object, to the extent of enabling a person skilled in the art to carry it out (see Guidelines for Examining Patent Applications, Block I). The 'object' is understood to be the subject matter for which protection is sought, that is, the subject matter contained in the set of claims. Accordingly, the analysis of full disclosure of the matter claimed must be evaluated based on what was disclosed in the specification, listing of sequences and drawings (as applicable).

When the application pertains to a product or process involving a biological material, which cannot be described such that a person skilled in the art can understand and reproduce the subject matter, then the specification must be supplemented by depositing said material (see item 2.2.1).

Two examples of lack of full disclosure (insufficient description) in the Field of Biotechnology warrant special attention. The first is that in which the embodiment of the invention depends on chance. In this situation, even if the person skilled in the art were to follow the instructions given in the application,

there is no guarantee of obtaining the contended results. These cases must be contested as a result of the provision laid down in Art. 24 of LPI (see item 2.2.1.1 and example 4). The second is when the embodiment of the invention is inherently impossible. For example, in a method which includes the amplification of a certain DNA sequence by using a given pair of primers, wherein said primers are not complementary to any part of the DNA sequence, thus rendering the execution of the method unfeasible.

Example 4:
The application describes a mutant microorganism obtained by random mutagenesis with UV radiation. As obtaining the microorganism depends on chance, full disclosure of the microorganism will only be satisfied by depositing the microorganism (see item 2.2.1.1). The document of proof of deposit of the microorganism in question may be presented via explanations, during the technical examination, provided that the deposit of the microorganism occurred up to the application filing date (or priority date, as applicable). The microorganism obtained by UV-induced mutation thus deposited shall not apply to Art. 10 (IX) provided that there is no concrete evidence that the microorganism having that characteristic is noted in nature.

Example 5:
The application describes a new and inventive method of obtaining mutant microorganisms by random mutagenesis. Since the stages of said method are described in detail in the specification, it is possible for a person skilled in the art to reproduce the invention. Therefore, said method presents full disclosure, in compliance with the provision in Art. 24 of LPI. If this method is tied to obtaining just one mutant with specific characteristics, the information on the deposit thereof must be included in the claim, since there is no guarantee of obtaining the same result.

Example 6:
The application describes a method which uses a mutant microorganism. The specification furnishes no details of the process of obtaining the microorganism, but characterizes it by way of its respective filing number. In this case, it is considered that a person skilled in the art could reproduce the method in question using the microorganism deposited. Accordingly, the invention meets the condition of full disclosure.

Example 7:
The specification discloses a protein by way of its access number at the NCBI database of sequences or by reference to a scientific article, and said protein

is essential for the embodiment of the invention. To comply with the requirement of full disclosure established in Art. 24 of LPI, the filing applicant is required to incorporate the sequence in question to the application, as disclosed in the databases at the time of filing/priority, in the form of listing of sequences, and this shall not result in the inclusion of subject matter, since said protein could be identified unequivocally from its access number or by way of the aforementioned scientific article (see additionally items 2.2.1.1 and 2.2.2).

Example 8:
The application describes a new dopamine receptor, duly characterized by its sequence of amino acids. The application mentions that antagonists and agonists of the receptor are also useful. Nevertheless, the application does not furnish a technical description of any antagonist and agonist compounds of the receptor. A person skilled in the art would not be able to carry out the invention related to the antagonists and agonists owing to absence of any technical instruction on how to do so, since the mere description of a receptor does not provide sufficient information concerning the molecules that might stimulate or prevent its working. Therefore, it is understood that the subject matters relating to the antagonists or agonists of the enzyme do not fulfill the condition of full disclosure (see also item 3.1).

2.2.1 Depositing biological material
In the case of biological material that is essential for the practical realization of the object of the application, which cannot be described in the form of Art. 24 and which is not publicly accessible, the specification shall be supplemented by depositing the material at an institution authorized by the INPI or recommended in an international agreement (Treaty of Budapest; see Guidelines for Examining Patent Applications, Block I).
Accordingly, it is considered that "biological material", in this context of deposit, may refer to any material containing genetic information capable of exercising direct or indirect self-replication. Representative examples include bacteria, archaea, protozoa, viruses, fungi, algae, seeds, lineages of animal and plant cell lines, hybridomas, artificial chromosomes and other vectors, and the host cell that harbors these biological materials, for some of these cases, and in accordance with the requirements of the chosen depositary center, can be deposited.

2.2.1.1 Cases in which the deposit of biological material must be carried out
It is important to emphasize, as mentioned above, that LPI refers to the deposit of biological material which cannot be described pursuant to Art. 24, that is, it cannot be described clearly and sufficiently in the specification. Thus, it is

concluded that the deposit of the material does not necessarily apply to any and all biological material involved in a particular invention, since, for example, polynucleotides and polypeptides shall be described by way of their nucleotide and amino acid sequences (N.B.: nevertheless, there is nothing to prevent such materials from being deposited in addition).

In relation to the microorganisms having different nucleotide sequences from that found in nature, the application shall present the modified nucleotide sequence by way of the listing of sequences (see item 2.2.2), or its name known in the art, or the deposit data of the microorganism. When essential to confer the inventive characteristic, the description must also include specific promoters, the insertion site of the heterologous material in the genome, the methodology of obtaining the sample, among other essential characteristics, such that a person skilled in the art is capable of carrying out the invention.

In cases where the microorganisms are selected from random mutagenesis and the genetic alterations which result in a differential effect are not defined in the application, then in order to comply with Art. 24 of LPI, the microorganism shall be deposited at an international depositary authority and the biological material deposit data (such as declaration of deposit or name of the institution, number and date of deposit) shall be included in the application (see item 2.2.1). Accordingly, the biological material will be available at the depositary authority and, therefore, will be considered clear, sufficiently described and reproducible. If the microorganism is not deposited, the subject matter will not comply with Art. 24 of LPI.

When the inventive characteristic obtained by genetic alteration is achieved only by a specific strain used in the application under examination, it is considered that the microorganism in itself is essential to carry out the invention and, therefore, the biological material shall be deposited so that the subject matter complies with Art. 24 of LPI. Moreover, depositing the biological material is not necessary when the inventive characteristic can be achieved by various strains or species of microorganisms available using the methodology described in the application. Thus, for situations where broadly known organisms are merely transformed to express a new and surprising characteristic, it is sufficient to indicate the organism of interest, relating it expressly to the nucleic acid to be used in this transformation, and to assure that this nucleic acid is described clearly and precisely.

In cases where the invention does not lie in a microorganism or biological material in itself, but rather in the use, modification or cultivation thereof, and a person skilled in the art is not capable of carrying out the invention without having said sample in the application, the deposit of the microorganism or the biological material is also necessary.

2.2.1.2 Timelines for depositing biological material

In connection with the original deposit of biological material for patenting purposes, IN PR N° 17/2013 establishes that the biological material shall be deposited by the filing date of the patent application, and that said data shall be included in the specification. In the event of a priority claim, the biological material shall be deposited prior to or by the date of the priority claimed, if applicable, that is, if the priority rights apply to the biological material.

When the data on proof of deposit of the biological material are not included in the patent application, and the examiner finds that such data are necessary, an office action shall be issued for the applicant to reply. If said office action is not complied with, then the application shall be rejected, based on Art. 24 of LPI.

2.2.2 Full disclosure of the listing of sequences

If the object of a patent application comprises one or more sequences of nucleotides and/or amino acids that are supported by the description of the invention, then the application shall contain a section of listing of sequences, with a view to achieving full disclosure as prescribed in Art. 24 of LPI (see Guidelines for Examining Patent Applications, Block I). It is emphasized that if the application uses and makes reference to sequences known in the art, and these are necessary for the embodiment of the invention, the examiner may issue an office action for the sequences to be presented. It must also be noted that the sequences shall correspond to those included in the state of the art at the time of filing/priority (i.e. as disclosed in the databases), bearing in mind possible refinement or alterations in the sequences over time.

Resolution INPI N° 228/09, incorporated into Resolution INPI PR N° 81/2013, provides for procedures for presenting the listing of sequences by electronic means and substitutes item 16.3 of AN 127/97 (see Resolution PR N° 81/2013 and its Appendices published in the Official Federal Gazette (DOU) – Section 1, N° 68, April 10, 2013).

2.3 Basis, clarity and precision (Art. 25)

2.3.1 Basis in the specification

The subject matter that is the object of protection shall be duly supported in the specification. Accordingly, the description in the specification shall furnish technical information capable of supporting all the subject matter claimed.

Example 9:

Claim 1: immunogenic protein characterized by consisting of SEQ ID:1, and fragments thereof.

The specification presents a mutated immunogenic protein (non-natural) having 600 residues of amino acids and also discloses an immunogenic fragment of this mutated protein (non-natural), determined as consisting of residues 320 to 400 of said protein. The set of claims, in turn, claims protection for the immunogenic protein and for immunogenic fragments of said protein (claim 1). However, the specification only discloses one immunogenic fragment of said protein, namely: which starts in position 320 and ends in position 400 of the protein. In this case, considering that the patentability requirements prescribed in Art. 8 of LPI were met, an office action shall be issued based on Arts. 24 and 25 of LPI so that the subject matter claimed is only restricted to that sufficiently described and effectively supported in the specification, namely the immunogenic protein and the fragment thereof that comprises residues 320 to 400 of said protein.

In this example, even if the filing applicant files new information regarding other immunogenic fragments of said protein which had not been described in the subject matter initially disclosed, such information could not be considered because the specification did not mention immunogenic fragments of the aforementioned protein other than that comprised between amino acids 320 and 400 thereof. Therefore, the fact remains that the claim for broad protection of "immunogenic fragments of the protein" cannot be accepted owing to the absence of full disclosure and support for the subject matter in the specification.

Example 10:

Claim 1: process for transforming plants characterized by introducing the gene X in angiosperms and gymnosperms.

The specification presents general information on the process and a detailed example of the transformation of the gene into an angiosperm. There is evidence for a person skilled in the art that said process would not be applicable in the same manner for both groups of plants, and therefore a claim which includes gymnosperms would not be supported in the specification. This lack of support might be overcome by evidence that the transformation of gymnosperms could be carried out under the same conditions already mentioned for angiosperms.

However, if to achieve support for the claim for gymnosperms the data furnished new parameters or any adaptations that are not trivial for a person skilled in the art, such information will not be accepted. This is because it would be necessary to include the data in the specification which would constitute the addition of subject matter, this being in disagreement with Art. 32 of LPI.

3. Claims

There are two basic types of claims: product, related to a physical entity; and process, related to an activity (see Guidelines for Examining Patent Applications, Block I).

In the Field of Biotechnology, some non-exhaustive examples of subject matters considered to be within the "products" category are: nucleic acids, peptides, polypeptides, proteins, microorganisms, virus, cells, vectors, plants, seeds, hybridomas, antibodies, probes, vaccines, compositions, kits, expression cassettes, extracts, food products, and others. For "process claims", some non-exhaustive examples are: process for producing a compound/composition; process for selecting a sequence of nucleic acid/polypeptides/peptides; process for producing a transgenic microorganism/plant/animal; method of purification; processes of extraction/isolation, among others.

3.1 'Reach-through' type claims in biotechnology

'Reach-through' claims are a special type of claim which seek protection for future inventions based on an invention from the present. That is, this type of claim seeks protection for inventions that had not been identified by the inventor up to the time of filing his patent application, but which may be identified in the future by use of the real invention.

A frequent type of reach-through claim in biotechnology is the product claim, said product generally corresponding to a "candidate compound". Such claims seek to protect compounds that are candidates for modulators of the activity of the real invention, such as the agents that modulate the biological function of a protein or a gene.

Reach-through products (drugs, agonists, antagonists, etc.) are usually identified merely by reference to a material or method used in the identification of same, without a definition of their chemical structures. Otherwise, such products are defined in terms of the function associated to the real invention, since this is the only information available to the inventor. Consequently, both compounds already known in the state of the art and those yet to be identified are ultimately encompassed within the scope of the claim, which thus become altogether broad.

The other type of reach-through claim in biotechnology is the process claim for identifying modulator compounds. In this type of claim, the compound identified by the process is not defined by its structure but rather by its capacity to modulate the expression of a protein or a gene involved in a disease, for example, or else by the screening method used to identify said compound. A common characteristic for these types of claims is that the subject matter that is the object to be protected is not known.

3.1.1 Technical examination of reach-through claims

The subject matters of the reach-through claims typically do not present full disclosure, clarity, precision and/or basis, thus being in disagreement with Arts. 24 and 25 of LPI.

Example 11:

Claim 1: Process for identifying an agonist/antagonist of polypeptide X characterized by comprising

(a) contacting said polypeptide with a compound to be screened; and

(b) determining whether the compound affects the activity of said polypeptide.

Claim 2: An agonist/antagonist characterized by being for the polypeptide X as identified by the process defined in claim 1.

The application pertains to a new and inventive process of screening for modulators of the activity of a polypeptide already known in the state of the art (polypeptide X), whose activity was demonstrated as involved in disease Y, though the compounds identified by said process were not characterized.

Claim 1 defines the main invention of the application which is a method of screening compounds of therapeutic interest and that modulates the activity of polypeptide X, being the actual invention, and claim 2 is of the reach-through type, which in this situation may include in its scope compounds already known and which are not modified at all by the process used in identifying same, and compounds not yet known.

Although the application sufficiently describes the screening process specified in claim 1, and from this aspect could be accepted, claim 2 is not accepted owing to lack of full disclosure (Art. 24), clarity, precision and support (Art. 25). Claim 2 uses functional (not structural) characteristics to define the subject matter that is the object of protection. It so happens that defining a product by functional characteristics often causes lack of clarity of the subject matter. A person skilled in the art could not reduce to practice to the definition of the subject matter object claimed, because the compounds claimed per se (claim 2) have potentially unlimited structural possibilities, and thus include compounds that are yet to be identified and/or that are already available in the state of the art and/or are barred by the prohibitions of Art. 10 (IX).Claim 2 seeks protection for candidate compounds identified by the screening method of the invention defined in claim 1. Said compounds were technically defined only by their activity (that is, functional definition – common wording in this type of claim) which in the present situation corresponds to a modulation (agonist/antagonist) of the activity of polypeptide X. The structural characteristics of the candidate compounds were not defined; said situation would oblige said technician to test innumerous compounds already known and all the compounds as may be identified in the future using the screening method of the invention, in order to determine which of these

compounds had the desired activity and that would thus be encompassed by the scope of the claims under examination.

4. Matter excluded from protection according to LPI

4.1 Definitions

According to the understanding adopted by this Institute, from the technical point of view, the terms and expressions used in these Guidelines are interpreted as follows:

- the "whole" (of natural living beings) refers to plants, animals, microorganisms and any living being;
- "part of natural living beings" refers to any portion of living beings, such as organs, tissues and cells;
- "biological materials found in nature" encompass the whole or part of natural living beings, in addition to extracts, lipids, carbohydrates, proteins, DNA, RNA, found in nature or isolated therefrom, and parts or fragments of same, as well as any substance produced from biological systems, for example hormones and other secreted molecules, viruses or prions. Synthetic molecules that are identical or indistinguishable from their natural counterparts are also encompassed within this definition;
- "isolated from nature" is understood to be all and any subject matter extracted and subjected to a process of isolation or purification, i.e. withdrawn from natural context;
- "genome" is the set of genetic information of a cell, organism or virus;
- "germplasm" is the set of hereditary material of a sample representative of individuals of a same species;
- "natural biological process" is any biological process that occurs spontaneously in nature and in which human intervention does not affect the end result;
- "therapy" is a treatment method designed to cure or prevent an infirmity or defective working of the body;
- "surgery" is defined by the nature of the treatment instead of its purpose, that is, it does not depend on manual or instrument intervention in the body of the patient having aesthetic or therapeutic purposes; and
- "diagnosis" refers to the identification of a particular disease.

4.2 Subject matters not considered inventions (Art. 10)

4.2.1 Natural biological products and processes (Art. 10 (IX))

In terms of "product" category claims, Art. 10 (IX) of LPI establishes that the whole or part of a natural living beings and biological materials found in nature, or isolated therefrom, including the genome or germplasm of any natural living being, are not considered to be inventions.

For "process" category claims, such as processes, methods, uses, applications, among others, Art. 10 (IX) of LPI refers solely to natural biological processes,

establishing that these not considered inventions.
Since Art. 10 (IX) of LPI addresses the whole or part of natural living beings and biological materials found in nature which are not considered inventions, documents published subsequent to the priority/filing date of the application under analysis can be used as evidence that the subject matter claimed does not comply with the provisions of Art. 10 (IX) of LPI, provided that the information available clearly and unequivocally proves that the subject matter claimed exists in nature.

4.2.1.1 Natural biological products

The whole or part of natural living beings and biological materials found in nature – even if isolated therefrom, or produced synthetically which have naturally- occurring correspondents, there being no way of distinguishing them from the natural ones –, are considered natural biological products, and are not considered to be inventions because they come under Art. 10 (IX) of LPI.
Accordingly, the inclusion of a disclaimer with the term "non-natural" in itself alone does not overcome the objection in terms of Art. 10 (IX) of LPI.

4.2.1.1.1 Compositions containing a natural biological product

A composition claim whose sole characteristic is the presence of a certain product also confers protection for this product in itself. Accordingly, a composition claim characterized solely by containing a non-patentable product (for example, a natural extract), cannot be granted, since it would protect the very non-patentable product. That is, even more so here than in cases of patentable components, the claim requires parameters or characteristics which unequivocally determine that it addresses a de facto composition.
In these cases, special care must be taken in connection to the text of the claim with regards the other component(s) of the composition in question, so as to prevent it from ultimately representing a mere dilution (an aqueous solution, for example) of the non-patentable product. Bearing in mind that the finality of a composition is to place the active component(s) in a suitable form for the purpose for which it is destined, a "mere dilution" would be one in which the solvent does not contribute to this end purpose, being merely the means used for extraction. Thus, it is possible that the aqueous or ethereal extract of a certain plant, for example, despite containing a component (extraction solvent) besides the extract itself, does not represent a ready composition to be used for its end purpose, and this same extract diluted in another solvent (used for, for example, to make the active ingredient absorbable) represents a de facto composition as opposed to a "mere dilution".

4.2.1.1.2 Extracts

Extracts are biological materials isolated from nature and, therefore, are not considered invention based on Art. 10 (IX).

Thus, for compositions containing extracts, the same considerations stated above apply for natural products.

4.2.1.1.3 Enriched extracts

Extracts differentiated from their natural correspondent by being enriched in any of their components will only be eligible for protection when their composition presents characteristics that cannot normally be achieved by the species and that result from direct human intervention.

Attention must also be paid to the case of extract of transgenic bacterial cells. Although the microorganism in itself may be patentable, its extract is not always patentable, since there may be cases in which it is not possible to distinguish the extract from the transgenic cell from the wild extract (for example, the transgenic microorganism merely superexpresses the endogenous protein).

Example 12:

Claim 1: A vegetable extract characterized by being enriched with isoflavones.

The extract is enriched with isoflavones by the isolation method. In this case, it is considered that a modification of said extract results from the simple fractioning of a natural extract isolated from nature, and said claim, therefore, comes under Art. 10 (IX).

Example 13: An extract enriched by genetic manipulation.

Claim: An enriched vegetable extract characterized by comprising human insulin.

The application describes a process of altering the composition of the plant extract by way of expression of the human insulin gene, resulting in an enriched extract. In this case, it is considered that the modification of said extract results from the genetic manipulation of the organism from which it is extracted. Thus, being a material obtained from plants which present characteristics normally unachievable by the species, resulting from direct human intervention, said extract is eligible for protection.

4.2.1.2 Natural biological processes

A "natural biological process" is understood to be any biological process that occurs spontaneously in nature and in which human intervention does not affect the end result.

If technical intervention performs an important role in determining the result, or if its influence is decisive, the process is considered an invention. That is, processes containing at least a technical stage that has a decisive impact on the

end result, and that cannot be achieved without human intervention, are considered inventions.

Under this concept, the classic process of obtaining plants or animals is not an invention. In the same way, processes only having stages which mimic events occurring in nature, are not considered inventions. In contrast, methods based on genetic engineering (for example, producing a transgenic plant), where technical intervention is significant, are eligible for patenting.

Microbiological processes encompass processes that use, apply to, or result in microorganisms. Although such processes are biological processes, the INPI considers that they are granted by being an exception from the legal exclusions permitted under the TRIPS Agreement (Art. 27(3)(b)).

In the same way, the INPI considers that biological or enzymatic processes for obtaining chemical compounds, presenting a technical stage that is decisive for the end result, are eligible for protection.

As in other processes, biological process claims formulated correctly define the base material, the product obtained and the means of transforming the former into the latter; the various stages necessary for achieving the intended purpose; or in the case of use, the material to be used and the purpose of the use.

Examples of suitable claims (N.B.: the level of detail necessary will depend on the specific invention under examination):

- Process for obtaining compound X characterized by cultivating microorganism W (bacteria, fungi, yeast, etc.) on Y.
- Process for obtaining compound X characterized by using enzyme E.
- Process for obtaining compound X characterized by cultivating cells of plant P transformed by gene T.

4.2.1.3 Use of natural products

When the process claimed involves the whole or part of natural living beings and biological materials found in nature, including the genome or germplasm, but does not consist of a natural biological process, there is no obstacle for the patentability thereof in light of that prescribed in Art. 10 (IX) of LPI. Accordingly, the use of a natural product can be eligible for protection, provided that is in accordance with patentability requirements.

Example 14:

Claim: Use of a natural resin obtained from Aloe vera plant leaves characterized by being for preparing cosmetic compositions for the treatment of keratin fibers.

Claims relating to the use of a natural resin for preparing cosmetic compositions can be accepted, with due regard for adherence to patentability requirements, since no article in LPI is contrary to the use of natural products in activities

that do not constitute natural biological processes.

Example 15:
Claim: Use of RNase characterized by being for cleaving the RNA.
Use of a natural material for carrying out the natural function itself is not considered an invention according to Art. 10 (IX), because it consists of a natural biological process.

4.3 Non-patentable inventions (Art. 18 of LPI)

4.3.1 Non-patentable inventions by violation of Art. 18 (I) of LPI

According to Art. 18 (I), "anything contrary to morality, decency and public safety, order and health" is not patentable.
Considering that biotechnology is an invention-generating technological field which addresses subject matter that may raise moral questions and issues of public order, current doctrine allows the INPI to reject the patenting of these inventions based on Art. 18 (I) of LPI.
Non-exhaustive examples include:(a) processes of cloning human beings;
(b) processes of modifying the human genome that cause modification of the genetic identity of human germinative cells; and
(c) processes involving animals that cause suffering thereto without resulting in any substantial medical benefit to human beings or animals from such processes.
In claims worded "process for cloning mammal cells", it is understood that the term "mammal" includes human beings. Thus, said claim might adversely affect morals, order and public health, and, therefore, would not comply with Art. 18 (I) of LPI. In this case, the exclusion of human mammals from the scope of protection would be an acceptable disclaimer, even if human beings are not excluded in the original specification.

4.3.2 Non-patentable inventions by violation of Art. 18 (III) of LPI

According to Art. 18 (III) of LPI, the following is not patentable: "living beings, in whole or in part, except for transgenic microorganisms meeting the three patentability requirements – novelty, inventive step and industrial application – listed in Art. 8 and which are not mere discoveries".
Regarding transgenic microorganisms, the sole paragraph of Art. 18 (III) of LPI defines that "For the purposes of this law, transgenic microorganisms are organisms, except all or part of plants and animals, that due to direct human intervention in their genetic composition express a characteristic that cannot normally be achieved by the species under natural conditions".
In accordance with this definition, the term transgenic microorganism covers microorganisms (see item 5) which are obtained by any technique having the

consequence of altering the genetic composition, that cannot be achieved by the species under natural conditions, by direct human interference. This definition is not limited to microorganisms which have exogenous genes and/or other organisms inserted therein.

In the examination of transgenic microorganism claims, it must initially be verified whether the term "microorganism" in the application description covers animal and vegetable cells, which is not eligible for protection, since the whole or part of plants and animals, even if transgenic, is not patentable. In these cases, the subject matter claimed must be limited so as to encompass only those transgenic microorganisms eligible for protection. Additionally, human intervention must be clear so that it is possible to evaluable whether it in fact addresses a microorganism that expresses a characteristic not normally achievable by the species under natural conditions.

Denominations such as "transgenic", "mutant" or "variant" are not sufficient to evaluate the patentability of the microorganism, in view of the possibility that the microorganism, even so-called "transgenic", "mutant" or "variant", may occur naturally or be indistinguishable from the natural one, and therefore not constitute an invention according to Art. 10 (IX) of LPI.

5 Microorganisms

The generic term "microorganism" is employed for bacteria, archaea, fungi, single cell algae not classified in the Plant Kingdom and protozoa. Accordingly, among the whole or part of living beings, natural or transgenic, LPI only allows transgenic microorganisms to be patented.

Examples of suitable formulations for microorganism claims (non-exhaustive list)

• Transgenic microorganism characterized by containing SEQ ID NO: X.

• Transgenic microorganism characterized by containing SEQ ID NO: X inserted in position Y of the genome.

• Transgenic microorganism characterized by containing sequence xxxxxxx in position Y of the genome (see item 2.2.2).

• Transgenic microorganism characterized by containing gene X (provided that the gene is well known).

• Transgenic microorganism characterized by containing gene X with the promoter Z inserted in position Y of the genome (provided that the gene and the promoter are well known).

• Transgenic microorganism characterized by containing expression vector X (provided that this vector is well known).

• Transgenic microorganism characterized by being the ATCC-XXXX (filing number).

Attention must be paid when SEQ ID NO: X, the gene X or the plasmid X were isolated from a natural and non-modified microorganism. In such case, the claim bearing the generic title of "microorganism" or "bacteria", among others, will also protect the original microorganism that has said gene naturally, and an objection will be admissible based on prescribed in Art. 10 (IX) of LPI.

6 Biological sequences

In general, in patent applications describing an invention whose development depends on sequences of amino acids and/or nucleotides, the following aspects shall be noted: (i) need to include the sequence in the application for purposes of full disclosure (Art. 24); (ii) natural occurrence (Art. 10 (IX)); (iii) clarity, precision and grounds (Art. 25) in the form in which such molecules / sequences are claimed; (iv) novelty (Art. 11); (v) inventive step (Art. 13); and (vi) industrial application (Art. 15).

Full disclosure of biological sequences is specifically addressed in item 2.2.2.

The novelty requirement, when related to biological sequences, follows the same general principle (see Guidelines for Examining Patent Applications, Block II), that is, for a sequence of amino acids or nucleotides not to be new in light of the state of the art, all the amino acids or nucleotides shall be exactly the same and be in the same order and, in some cases, additionally have the same structural formula as the sequence known in the art.

The further points in which unsuitable matters are usually noted will be addressed in the topics below.

6.1 Characterization

Once the rules established in item 2.2.2 have been observed in order to guarantee clarity and precision of the subject matter claimed, the set of claims shall refer to the biological sequences in question by way of the corresponding SEQ ID NO: (see item 2.2.2).

In some cases, other forms characterizing biological sequences can be accepted:

a) when the sequences have fewer than four amino acids or ten nucleotides, in accordance with Resolution PR N° 81/2013, they shall be characterized by the sequence itself;

b) structural formulae accompanied by their corresponding SEQ ID NO: ;

c) Markush formulae accompanied by their corresponding SEQ ID NO: ;

d) deposit number (see item 2.2.1); or

e) by its name or designation, when a biological sequence is already known in the state of the art and is not the main object of the invention.

It is emphasized that a DNA must be defined by its sequence of nucleotides, whereas a protein, by its sequence of amino acids, so as to define with clarity the subject matter that is the object of protection.

Additionally, attention must be paid to claims of the following types, since none of them bears clarity (Art. 25).

a) DNA sequence characterized by encoding a protease.

In this type of claim, the product is characterized solely by its function, which is not sufficient to define with clarity what the product refers to. In contrast, if this DNA is characterized by its sequence of nucleotides, the definition of

the function may be accepted, as an additional characteristic of the product.
b) DNA sequence characterized by encoding a polypeptide presenting a sequence of amino acids of the protein represented by SEQ ID NO: 1.
This wording defines a DNA by the sequence of amino acids, which is not permitted. However, the claim may be altered so as to define the DNA by the sequence of nucleotides, and their degenerations which generate the same protein may be accepted. In this situation, at least one sequence of nucleotides must be present in the application as filed, unless it is a sequence that is already available in the state of the art and referenced in the specification.
c) Protein characterized by presenting activity Y.
The product is characterized solely by its function, which does not enable the scope to be clearly defined. In contrast, if said protein is characterized by its sequence of amino acids, the definition of the function may be accepted, as an additional characteristic of the product.
d) Protein with activity Y characterized by presenting the following composition in amino acids: (percentages of each amino acid present).
In this type of claim, the product is characterized by its function and by the percentage of amino acids, which does not enable the product claimed to be clearly defined either. The sequence of amino acids is necessary.
e) Plasmid characterized by being the pWn.
In this type of claim, the product is characterized by a designation given by the inventor himself, which does not permit the product to be defined.

6.1.1 Markush form sequences

Biological sequences can be presented in the form of a Markush formula containing a base sequence that is substituted by one or more variable substructures, which are accompanied by a list of definitions of these variable portions, such as, for example:
Peptide of Formula I
Xaa1 Xaa2 His Xaa4 Pro Gly Ser Phe Ser Asp Glu Gly Asp Trp Leu; wherein
Xaa1 is His or Thr;
Xaa2 is Ala, Gly or D-Cpa (4-chloro-Phe); and Xaa4 is Gln, Asn or Pro.
For further details on Markush formulae, see the Guidelines for Examining Patent Applications, Block II.

6.1.2 When it is necessary to file the listing of sequences in conjunction with the application

Resolution PR N° 81/2013 of the INPI establishes in Art. 2 thereof that when the patent application contains one (or more) sequence(s) of nucleotides and/or amino acids, which is (are) fundamental for the description of the invention, said sequence(s) shall be presented in a listing of sequences.

When the invention includes the sequence per se, that is, when the set of claims bears "protein", "polypeptide", "nucleic acid" claims, or any other term designating a biological sequence, such is considered a fundamental part of the invention, and must be included in the listing of sequences (except for sequences having fewer than four amino acids or ten nucleotides, cf. defined in Resolution PR N° 81/2013).
In contrast, when a molecule in question is solely an illustrative example, said specific sequence may not be considered a fundamental part of the invention, and therefore, its sequence does not necessarily need to be presented as part of the application.
Additionally, care must be taken regarding the possibility that other sequences used in the application – and not necessarily the encoding genes / sequences – are fundamental to carry out the invention. Thus, in these cases, it is also important to evaluate whether the sequence in question is broadly known in the art, and whether its use is fundamental to carry out the invention.

6.1.3 Need to restrict the set of claims to the sequences filed in conjunction with the application

When a sequence in question solely represents a molecule that is part of a process described, but that any other molecule having the same biological function would present the same result (or in situations where there is no reason to believe that such molecules would not be effective), said method does not necessarily have to refer to a single SEQ ID NO:, since said measure would unnecessarily restrict the scope of the method in question.

Example 16:

The application describes a method of inducing sporulation in bacteria characterized wherein said bacteria are transformed with a vector containing a sporulation gene under the control of any promoter. The examples presented in the application use the spo5 gene. Nevertheless, any gene of the spo family would theoretically allow the same result to be achieved. Thus, in theory, there is no reason to demand that a specific sequence of the spo5 gene be presented in said method claim.
Attention in these cases should lie on the "generic" name given to the sequence of interest, the so-called "spo gene", as mentioned above, because if the applicant uses said denomination in the claims, it must be broadly known and used in the art, unequivocally referring to a certain gene family.

Example 17:

A method for inducing the expression of a given gene under certain specific conditions.

The specification clearly states that the desired characteristic is a genic expression in a certain condition, which is only obtained by use of promoter X, since this promoter is only activated when the medium impacts the characteristics of interest (depletion of glucose, for example).
The application describes the use of different genes under the control of this promoter X, demonstrating that they are all expressed solely in the conditions of interest.
In this case, the single fundamental sequence to obtain the desired characteristic is that of promoter X. Thus, as in the prior example, it is considered that the presentation of the sequences of genes used is not compulsory; and even if the applicant presented such sequences, it is not deemed necessary that the subject matter claimed be restricted to these genes. Nevertheless, the sequence of the promoter, which is the invention, must be described clearly and precisely by way of its corresponding SEQ ID NO:.

6.2 Homology versus identity

When aligning and comparing nucleotide or protein sequences with each other, the terms homology, identity and similarity may be employed. At this stage, it is important to make the distinction between such terms.
Two sequences (of nucleotides or amino acids) are homologous solely when they share a same common ancestor. Therefore, the concept of being "partially homologous" is non-existent: two sequences are either homologous or not, and it is incorrect to speak of percentage of homology. Homologous proteins generally share many similarities regarding their three-dimensional structures. When two sequences are homologous, they generally share a significant identity, though there may also be cases to the contrary: two molecules may be homologous without sharing a statistically significant identity between their sequences of amino acids or nucleotides (for example, as is the case of the family of globins).
Establishing homology between two sequences is not solely based on the analysis of the identity between these sequences, but also on biological criteria, such as analyzing the structure and function of the proteins, for example. Results from comparing sequences by way of algorithms such as BLAST, FASTA and SSEARCH do not evaluate homology between sequences: they measure the similarity and the identity between sequences. Whereas homology refers to a qualitative inference, identity and similarity are quantitative attributes.
The identity between two sequences refers to the occurrence of precisely the same nucleotides or the same amino acids in a same position in two nucleotide or protein sequences aligned and compared to each other. Therefore, if two proteins present 90% identity, this means that 90% of all the residues of amino acids contained in said proteins in corresponding positions are precisely identical.
In contrast, the percentage of similarity between two sequences of proteins refers

to the sum of the identical and similar matches (for example, the amino acids glutamate and aspartate are considered similar, since both are acidic). It must be noted that the similarity can be measured based on different definitions on how related (similar) an amino acid residue is to the other.

Applying these terms to the examination of patent applications, the following types of claims are not accepted:

a) claim of the type "protein (or DNA sequence) characterized by being a SEQ ID NO: 1 or any other sequence of amino acid with at least x% homology with SEQ ID NO: 1" is not clear (in disagreement with Art. 25 of LPI), since, technically, the term "% homology" is not applicable, as highlighted above; and

b) claim of the type "DNA sequence (or protein) characterized by presenting at least 80% identity (or similarity) with SEQ ID NO: 1" cannot be accepted since said as worded it covers innumerous different sequences, and also does not specify at which sites in the sequence of nucleotides (or amino acids) substitutions may occur; therefore, claims of this type cannot be accepted, since the characterization of the object of protection is not clear and precise, this being in disagreement with Art. 25 of LPI.

Furthermore, the characterization of the sequence of interest based on the identity percentage is highly broad and generally includes in its scope sequences not supported by the specification or that do not meet patentability requirements. Lastly, it is also important to note that in these cases, the specification does not generally provide sufficient information to enable the reproduction of all the countless sequences covered by said type of definition (this being in disagreement with Art. 24 of LPI).

6.3 Sequences of nucleotides

Nucleotide sequences can be referred to in patent applications in different forms: genes, vectors, plasmids, DNA sequence, RNA sequence, nucleic acid, oligonucleotides, primers, cDNA, and other. Nevertheless, for purposes of simplification, in these Guidelines, all these molecules will be designated, in general terms, as "sequences of nucleotides". This definition is valid despite the size of said molecule. The items below will address the particular aspects of some of these molecules.

Said sequences of nucleotides shall be characterized in accordance with the item 6.1. Nevertheless, it must be emphasized that the molecules defined by a sequence with fewer than ten nucleotides shall be characterized by the sequence of nucleotides itself.

6.3.1 Modification of nucleotide sequence(s)

Modifications in nucleotide sequences with the aim of differentiating them from natural sequences may be carried out in different ways. In theory, any

characteristic introduced into the sequence that was not described as naturally-occurring is acceptable as a modification so as to comply with Art. 10 (IX) of LPI, with due regard for that prescribed in item 6.3.1.1. Nevertheless, the simple introduction of terms such as "recombinant" in natural molecule claims cannot be accepted, since the resulting molecule would be indistinguishable from its natural counterpart, even if produced in recombinant manner.

6.3.1.1 Modification of sequence(s) by substitutions, insertions or deletions of non-modified nucleotides

In general, modifications of natural biological sequences by inserting non-modified nucleotides into the sequence (in the middle or at the ends) are considered sufficient so as to comply with Art. 10 (IX), provided that the resulting sequence formed is not naturally-occurring either.

If nucleotides are deleted in the middle of the sequence claimed, said modification is, theoretically, enough to differentiate it from the natural molecule. Nevertheless, even in cases where deleted nucleotides are contiguous and are at the end of the sequence, this still does not comply with Art. 10 (IX), since the resulting sequence is still identical to part of the natural sequence (see item 6.3.2).

Regarding the substitution of nucleotides by other non-modified nucleotides, it is considered that said modification is sufficient to comply with Art. 10 (IX), provided that there is no description of natural sequences (for instance, in related species) containing said substitution.

Nevertheless, it should be considered that various substitutions of nucleotides in a given sequence may not result in any modification in the protein encoded thereby, owing to degeneration of the genetic code. Thus, in these cases, a nucleotide sequence modified by substitutions may comply with Art. 10 (IX), whereas the sequence of amino acids encoded thereby remains identical to the natural one, and, therefore, does not comply with Art. 10 (IX).

When analyzing sequences derived from the state of the art, which comply with Art. 10 (IX), it is important to analyze the inventive step of the modification (insertion, deletion or substitution) made, taking into account the fact that some groups of amino acids present common properties. Thus, the inventiveness of these alterations in the polynucleotide sequences generally depends on the demonstration of an unexpected effect generated by the modification in relation to the state of the art.

6.3.1.1.1 SNPs

The SNP abbreviation refers to "single nucleotide polymorphism" and is used to designate natural variations that occur in the genome and which involve, as the name suggests, a single nucleotide. They may be associated to certain

characteristics, thus acting as molecule markers.
Regardless of the utility described, whenever a certain SNP – or any other polymorphism – is described as being naturally-occurring, it cannot be considered as an invention, according to Art. 10 (IX) of LPI. Nevertheless, the use of a set of SNPs, for example, in an in vitro diagnosis method (such as DNA fingerprinting) or in the ambit of personalized medicine, may be eligible for patent protection.

6.3.1.2 Modification of sequence(s) of nucleotides with modified derivatives (including protector groups)

Inserting nucleotides that are not naturally-occurring (derivatives of natural nucleotides) are also considered sufficient modifications for the sequences to comply with Art. 10 (IX). Nevertheless, the presence of these nucleotides and the list of nucleotides of interest shall be expressed in the claims, so as to prevent the natural nucleotides from being indirectly included whereby resulting in the natural biological sequence.
The inclusion of such nucleotides in the sequences presented in patent applications is addressed in INPI Resolution PR N° 81/2013, cited in item 2.2.2 of these Guidelines; and a list with examples of modified nucleotides and the acceptable abbreviation in their definition is available in Table 2 of the Appendix to this Resolution (published in the Official Federal Gazette (DOU) – Section 1, N° 68, April 10, 2013).

6.3.2 Fragments

Special attention is required in analyzing claims involving "Fragments of sequences", even if such sequences are inserted into the application. Said consideration is due to the fact that the definition of "fragments" of a said sequence includes all and any subdivision of the sequence presented, resulting in an undefined number of possible fragments, which do not present any function/relation with the subject matter described in the application.

Example 18:
An application presents SEQ ID NO: 1 (hypothetical): agctggttcgactgtctcga.
The claim refers to a "nucleic acid characterized by having a sequence of nucleotides of SEQ ID NO: 1 and fragments thereof". As the claim stands, said claim includes, for example, molecules such as: agct, actg, ctgg, ggtt, ggttc, cgactgt, and an infinity of others, including many that do not have any function described/related with the invention.
Thus, it is clear that the reference to fragments of a given sequence cannot be accepted in the claims, since the subject matter claimed is not supported, nor is it clearly and precisely defined in accordance with Art. 25 of LPI. In these cases, full disclosure of the subject matter may be questioned in accordance with Art.

24 of LPI.

On the other hand, if the application describes that fragments obtained from a certain sequence are useful to the finality described in the invention, such fragments may be claimed, provided that the desired fragments are clearly identified in the claims (specifying the position of the initial and final nucleotides of this fragment) and are not natural.

6.3.3 Oligonucleotides (or primers)

Since they represent segments of sequences complementary to genes and/or natural mRNAs, it is considered that primers are part of natural biological material, and therefore, claims that claim such primers do not comply with Art. 10 (IX) of LPI (note the possible exceptions in item 6.3.1).

6.3.3.1 Degenerate and modified oligonucleotides

Degenerate oligonucleotides generally consist of a mixture of oligonucleotides which can be used for amplifying genes that have similar but not identical sequences (such as the amplification of orthologous genes in related species), or same genes unknown.

Attention must be paid to the possibility that one (or some) of the resulting oligonucleotides are identical to a natural biological sequence (for example, to the gene sequence intended for amplification), which in this case does not comply with Art. 10 (IX). On the other hand, if they present modifications, which result in a different sequence of nucleotides to that which occurs in nature, they will comply with Art. 10 (IX) (see item 6.3.1).

Additionally, considering that a mixture of oligonucleotides (for example, degenerate oligonucleotides, etc.) may not be clearly and precisely defined, the claims relating to this subject matter will not comply with Art. 25 of LPI. Attention is also needed for the description of this mixture in the specification (compliance with Art. 24 of LPI).

Furthermore, so that the subject matter claimed is clearly and precisely defined, a degenerate oligonucleotide may be characterized based on a consensus sequence, and vary solely by one or a few pre-defined nucleotides. In such cases, the claims relating to these degenerate oligonucleotides shall cite the consensus sequence and the variable nucleotide positions.

6.3.4 Promoters

Promoters are the central processor of the regulation of a gene, since it contains the binding sites for the RNA polymerases, responsible for the genic transcription. By definition, it comprises the region 5' of the gene. The processes that provide the transcriptional modulation are highly complex and occur by way of an intricate

network of interactions involving regulatory sequences (TATA box, CCAAT box etc.) and other elements located further away from the transcription starting point (enhancer and silencer sequences).
Contrary to gene sequences, which have specific "markers" for their start and finish (for example: initiation codon, site for polyadenylation, etc.), the sequence of a promoter does not present such delimitations. Therefore, experimental data shall be presented to prove that the isolated DNA sequence is indeed capable of leading to the expression of gene sequences, that is, it shall present the promoter activity of interest.
There are intermediary cases in which the DNA sequence with promoter potential is isolated, sequenced and analyzed by bioinformatics to predict its possible regulatory motives (CCAAT box, TATA box, CpG islands, etc.). Said analysis in silico, though of great importance for preliminary studies, is not sufficient to demonstrate that the sequence identified is indeed a promoter region, validation with suitable functional assays being necessary.
In any case, as they are made up of sequences of nucleotides, promoters shall be represented by a SEQ ID NO: X, as established in items 2.2.2 and 6.1.2.

Example 19:
Claim 1: DNA sequence characterized by being SEQ ID NO: 1
Said sequence was isolated and presents promoter activity: said claim cannot be accepted because it does not comply with Art. 10 (IX) of LPI.
Nevertheless, in cases where the SEQ ID NO: 1 presents mutations, deletions and/or insertions, that is, it becomes different to the sequence as found in nature, the examination of novelty, inventive step and industrial application of the invention is applicable. It is important to note that deletions may result in fragments that are considered as part of the natural material, and therefore, would not comply with Art. 10 (IX) (see items 6.3.2 and 6.3.3.1) either.

Example 20:
Claim: Expression cassette characterized by comprising the promoter sequence of SEQ ID NO: 1 operationally bound to a gene of interest and a terminator sequence.
If SEQ ID NO: 1 was found in nature, but was subsequently modified (via punctual mutations, deletions and/or insertions), the above claim may be accepted, provided that the subject matter is considered new and inventive. If SEQ ID NO: 1 is as found in nature, the claim must be restructured so as to better specify the cassette, with the introduction of the term "heterologous", clearly stating that it does not cover protection for subject matter that does not comply with Art. 10 (IX) of LPI (see item 6.3.5).

Example 21:

Claim: Expression cassette characterized by comprising a promoter sequence selected from the group of SEQ ID NO: 1 to 3 or fragments and derivatives thereof operationally bound to a gene of interest and a heterologous terminator sequence. This type of claim must be analyzed taking into account the observations in the examples above. Furthermore, the promoter sequence must be restricted solely to the sequences for which the promoter activity of interest was demonstrated. If promoter activity was demonstrated solely for SEQ ID NO: 1, for example, a claim must be limited to said sequence; further, the term "or fragments and derivatives thereof" cannot be accepted, since the subject matter claimed is not supported, nor is it clearly and precisely defined in accordance with Art. 25 of LPI. In these cases, full disclosure of the subject matter may be questioned in accordance with Art. 24 of LPI.

6.3.5 Vectors

A vector is a DNA molecule used as a vehicle for transferring exogenous genetic material to other cells. Normally, DNA vectors present three characteristics: (i) they contain an origin of replication that enables the replication thereof, regardless of the host chromosome; (ii) they contain a selection marker that enables the cells containing the vector to be easily identified; and (iii) they present single sites for one or more restriction enzymes. The cloning vector is designed to replicate an insertion in a host cell. The expression vector contains an expression cassette that enables the insertion to be expressed in the target cell in an induced or constitutive manner. The expression cassette contains regulatory sequences, such as transcription promoter and terminator sequences.
Regarding full disclosure pursuant to Art. 24 of LPI, the examiner shall analyze the invention in question and the level of detail necessary for it to be reproduced, depending, for example, on whether the vector is the main invention or an accessory invention. In this sense, certain aspects shall be noted in the specification:

- representative drawing of the map of the vector in question, highlighting the essential characteristics for it to work, that is, the cleavage sites for the restriction enzymes, the appropriate restriction enzymes, the promoter used, the repression regions, the termination regions, the marker sequences or sequences that confer resistance to antibiotics, etc.;
- the sequence to be cloned and/or expressed in the form of SEQ ID NO: X shall be present in the listing of sequences, pursuant to the Resolution(s) in effect;
- if the preferred codons for expressing the insertion in a given microorganism are essential to the invention, they must appear in the listing of sequences; and
- the procedures and the conditions for manipulating the DNA/RNA, including the enzymes used (for example, endonuclease, polymerase, ligase, etc.), the cloning systems involved, the conditions of transfection/transformation of the host cell, among other usual techniques.

It is important to point out that when there is no other way of defining the vector in reproducible form (full disclosure – Art. 24 of LPI), the biological material must be deposited (see item 2.2.1).
Below are examples of claims designed to reflect commonplace situations in which vectors are recombinants. In other words, these examples do not encompass natural vectors found in bacteria, fungi and plants, especially in mitochondria and chloroplasts, since these are not considered inventions in light of Art. 10, item IX, of LPI.

Example 22:
Vector as main invention.
Claim: A vector characterized by consisting of filing number XXXX.
The main invention pertains to a new and inventive vector which can be employed for cloning and/or expressing a gene of interest. In this case, the vector can be characterized in a claim by its filing number recorded at an International Depositary Authority. Therefore, the vector will be defined clearly and precisely, pursuant to Art. 25 of LPI.

Example 23:
Vector as main invention.
Claim: A vector that contains the sequence of origin of replication, selection marker sequence and multiple cloning sites characterized by comprising SEQID NO: X
In this example, the structure of the vector is new and inventive owing to the specific combination of SEQ ID NO: X with the other elements common to vectors, such as the sequence of origin of replication, the selection marker sequence (for antibiotics, etc.) and the sites for the restriction enzymes. Therefore, the essential elements that distinguish this vector from others in the state of the art shall be the only elements characterized by their respective SEQ ID NO: X, since the other components are known by a person skilled in the art. Importantly, in this case, the SEQ ID No: X does not correspond to the expression cassette.

Example 24:
Vector as an inter-related invention.
Claim: Vector characterized by comprising the sequences defined by SEQ ID NO: X and SEQ ID NO: Y operatively bound to the heterologous promoter and terminator sequences.
The invention describes two genic sequences involved in the transport of lysine which were isolated from Corynebacterium glutamicum. SEQ ID NO: X encodes the lysine-exporter protein (LysE), whereas SEQ ID NO: Y encodes the LysE regulator protein (LysG). Although SEQ ID NO: X and SEQ ID NO: Y are endogenous to the host

cell Corynebacterium and are therefore natural, they are flanked by heterologous sequences of the gene construction present in the recombinant vector. Accordingly, the vector complies with that prescribed in Art. 10 (IX) of LPI.

Example 25:

Vector as inter-related invention.

Claim: A vector characterized by comprising a DNA construction consisting of the sequence defined by SEQ ID NO: X operationally bound to the transcription promoter and terminator sequences.

The invention refers to a new gene sequence which bears inventive step and is eligible for cloning/expressing in suitable host cells.

In cases where SEQ ID NO: X is identical to that found in nature, care must be taken such that the construction as a whole presents some heterologous sequence as a way of differentiating it from the natural sequence. However, if SEQ ID NO: X is altered, the term "heterologous", as used in example 24, is not necessary.

6.3.6 cDNA

cDNA molecules represent sequences produced from RNAs. In the case of cDNAs originating from messenger RNA (mRNA), if the originating gene has introns, the cDNA will be different to the gene that encoded this mRNA, since the cDNA sequence will only present the sequence of exons. Accordingly, in these cases, it cannot be considered that a cDNA molecule is identical to a natural molecule, and its patentability must be evaluated based on the requirements of novelty, inventive step and industrial application.

When the cDNA addresses molecules produced from mRNAs from genes that do not have introns, said cDNA will have an identical constitution to the DNA/gene strand which acted as mold for synthesizing this mRNA. Thus, in these cases, the cDNA is not considered an invention, according to Art. 10 (IX) of LPI.

In cases of cDNA obtained from other types of RNA (such as, for example, tRNA, snRNA, rRNA), it must be verified whether they are identical to the natural DNA, a situation in which they would not be considered an invention, according to Art. 10 (IX).

Additionally, the simple sequencing of the cDNA without association of a function for same, is not sufficient to guarantee industrial application (see item 1.1) and support for the subject matter, this being in disagreement with Arts. 15 and 25 of LPI, respectively.

6.3.7 ESTs – Expressed Sequence Tags

The term "EST" refers to a partial sequence – or a fragment of the sequence – obtained from a cDNA (hence the fact of referring solely to expressed sequences). The simple sequencing of an EST is not sufficient to guarantee industrial

application and support for the subject matter, this being in disagreement with Arts. 15 and 25 of LPI, respectively.
Additionally, so as to comply with Art. 10 (IX), the analysis of this subject matter follows the same criteria used for cDNA; therefore, it is necessary to know whether said EST represents a sequence fragment of a single exon (in which case it would be considered part of a natural biological material), or if it extends beyond the juncture point between two different exons (in which case there would be no natural equivalent, and therefore, could be considered as an invention).
In contrast, when addressing sequences originating from genes that do not have introns, any EST is considered a fragment of a natural biological sequence (see also item 6.3.2).

6.3.8 ORFs – Open Reading Frames

The term ORF refers to potentially encoding sequences, generally obtained from DNAs sequencing. Additionally, an ORF has an initiator codon (relating to a methionine, for the majority of organisms) and ends with a terminator codon.
Since this is a region of the genome, the ORF is deemed to be a natural product, and is not considered an invention according to Art. 10 (IX).
An ORF represents a candidate to an encoding region of a genome that does not necessarily result in a functional gene product. Thus, in the case of a claim of the type "vector characterized by comprising an ORF present in SEQ ID NO: 1", it is important to evaluate the demonstration of the functionality of the product obtained from the expression of this ORF, in order to meet the requirement of industrial application (Art. 15), as well as clarity and precision of the subject matter claimed (Art. 25).

6.3.9 RNAs

RNAs encoded by natural genes are also natural biological molecules, and therefore, are not considered inventions according to Art. 10 (IX) of LPI.
In contrast, if they are a product of the expression of chimeric genes (such as genes constructed to express fusion proteins and/or others in existence not found in nature), such RNA molecules, cannot be considered a natural biological material.

6.4 Sequences of amino acids

For definition purposes, it is considered that in analyzing patent applications, "proteins", "peptides" and "polypeptides" shall be defined based on their linear sequence of amino acids (primary structure), regardless of their size (total number of residues of amino acids in accordance with Resolution PR N° 81/2013). Therefore, citing any one of these terms ("proteins", "peptides" or "polypeptides") in these Guidelines generally refers to a "sequence of amino acids" or "protein sequence".

6.4.1 Characterization of sequences of amino acids

As stated above, having followed the rules established in items 2.2.2 and 6.1, as a form of guaranteeing clarity and precision of the subject matter claimed, the set of claims shall refer to the proteins in question by way of corresponding SEQ ID NO: and in some cases, additionally, by their structural formula. Sequences with up to 03 (three) residues of amino acids shall be represented throughout the application solely by their sequence.

Example 26: Acceptable claims for sequences of amino acids (provided that these sequences are not naturally-occurring).

Claim: Protein X characterized by comprising a sequence of amino acids as defined in SEQ ID NO: 1.

Claim: Polypeptide characterized by consisting of a sequence of amino acids as defined in SEQ ID NO: 1.

Claim: Protein X characterized by consisting of the sequence SEQ ID NO: 1.

Example 27: Claim not acceptable for sequences of amino acids.

Claim: Protein characterized by consisting of a sequence of amino acids encoded by SEQ ID NO: 2 (sequence of nucleotides).

In this situation, an office action shall be issued for the applicant to state the sequence of amino acids corresponding to the sequence of nucleotides presented, without constituting the addition of subject matter.

Accordingly, the characterization of protein sequences solely by way of their properties, such as three-dimensional structure, function or biological activity, name, chemical properties (PI, molecular weight, composition of amino acids, etc.) will not be accepted in the claims, since the only way of clearly and precisely defining a sequence of amino acids in an unequivocal manner is by the sequence itself.

Additionally, attention must be paid to item 6.2 of these Guidelines, which address biological sequence claims by way of percentage of identity and/or similarity to a sequence of reference.

It is important to bear in mind that the use of the terms consist or comprise results in differences of scope of the claim (see the Guidelines for Examining Patent Applications, Block I).

Example 28:

The specification of the application describes a mutated protein (non-natural) characterized by consisting of SEQ ID NO: W. In this case, it would not be possible to accept a generic claim that sought protection for the mutated protein (non-natural) characterized by comprising SEQ ID NO: W, as this would imply the

possibility of having any extension in the carboxyl and/or amino terminal regions of the protein that might cause alterations to the three-dimensional structure of same and/or alterations of function. Therefore, it would not be possible to assert that any protein comprising SEQ ID NO: W would work in a similar way to the consisting of SEQ ID NO: W, and said claim shall be questioned owing to the lack of full disclosure and support in the specification (Arts. 24 and 25 of LPI). Even if the specification discloses certain possible extensions in the sequence of amino acids of the protein, such examples would not be sufficient to support that any extension would achieve the same result.

6.4.2 Homologous proteins (paralogous versus orthologous)

Homologous proteins are proteins that derive from "common ancestral evolution". They may be present in a same species, being derived from gene duplication, originating what is called paralogous (equivalent proteins – with or without sequence alterations produced during the course of evolution – present in a same species). Moreover, they may be present in different species and that have common ancestry; in this case, such proteins are called orthologous.

These definitions are important for evaluating the inventive step of applications that describe and claim proteins similar to proteins whose function is already known, differing solely in relation to the organisms from which the protein originates.

Example 29:

The patent application describes protein B, isolated from a certain species. This protein B presents sequence and activity that is highly similar to another protein, called A, previously described in the state of the art for a different species (A and B are, therefore, orthologous proteins). In these cases, it is considered that the simple fact that protein B is isolated from a different organism does not necessarily make it inventive in light of protein A. Thus, the evaluation of inventive step may consider whether protein B presents any unexpected characteristic in light of its orthologous A. Even so, in this case, protein B in itself would not be considered an invention according to Art. 10 (IX).

Additionally, when the applications involve "variants" or "modifications" of proteins natural, attention must be paid for compliance with Art. 10 (IX), since such "modifications" may result in another provably natural biological molecule, originating solely from a different species to the one described in the application.

Example 30:

An application describes modifications in a bovine protein so as to render it suitable for a certain use, and claims the modified protein itself. Nevertheless,

the protein resulting from the alterations introduced, for example, substitutions, results in a sequence identical to that of the canine version of said protein, which is already known. In this case, even though it is not identical to the natural equivalent of the organism in which it was obtained, the protein claimed is identical to an orthologous protein – natural from another species –, and, consequently, does not comply with Art. 10 (IX) either.

6.4.3 Protein fragments

A protein fragment, in the same way as a protein, must be characterized at least by its sequence of amino acids (see item 6.4.1). Accordingly, when a protein fragment is claimed, and characterized solely by its sequence linear, the examiner must perform a search by the characterizing sequence of amino acids. If a sequence is found in the state of the art as part of a protein or peptide of natural origin, the subject matter claimed will not comply with Art. 10 (IX) of LPI, because it constitutes a part of natural living beings and/or biological materials found in nature.

When a peptide containing few amino acids is claimed, it is likely found in a protein in nature, even without a known function in the protein or in a different context to the subject matter presented in the application under examination. Even so, the subject matter claimed relates to the provision of Art. 10 (IX) of LPI, since no delimitation is established in LPI regarding a minimum size for a fragment to constitute a part of a natural biological material. Therefore, any part of natural living beings and biological materials (i.e. fragments) found in nature shall not be considered to be an invention.

It is possible for a fragment claimed to be identical to a part of the whole molecule found in nature. In these cases, even when the fragment claimed presents innovative activity, function, or chemical properties in light of the state of the art, since it constitutes a part of a natural living being or a biological material found in nature, it is not an invention according to Art. 10 (IX) of LPI, so it is inappropriate to perform any type of analysis regarding its novelty and inventive step.

It is important to note that the presence or inclusion of the term “recombinant” in a natural molecule claim cannot be accepted, since the resulting molecule would be indistinguishable from its natural counterpart, even if produced in a recombinant manner.

Therefore, it is clear that any portion of a protein found in nature, regardless of the number of amino acids, must be considered a part of natural living beings and biological materials found in nature and, therefore, is not considered an invention according to Art. 10 (IX) of LPI.

Example 31:

Claim: Peptide characterized by the sequence Ile-Leu-Arg.
Protection is claimed for a biologically active peptide, obtained synthetically, with immune-regulatory properties, comprised of three amino acids. The search revealed that the sequence is contained in various natural proteins. The application contends that the peptide may be different to the natural polypeptide from various aspects such as folding, spatial conformation, aggregation and physical-chemical properties. Although there are differences in the physical-chemical properties of the molecule claimed with relation to natural polypeptides that comprise the same sequence, the peptide claimed presents a sequence of amino acids found in nature, and this is why the subject matter is not considered an invention according to Art. 10 (IX) of LPI.

Example 32:
Claim: Protein characterized by presenting SEQ ID NO: 1 wherein positions 1 to 6 have been deleted.
A cytokine having 76 amino acids when truncated in the sixth amino acid amino-terminal begins to display antagonist activity of the whole cytokine and thus can be used to manufacture medicines to treat diseases wherein a cytokine antagonist is needed. Although human interference resulted in an innovative activity, said fact was solely due to the deletion of part of the molecule, maintaining the sequence obtained identical to the sequence of amino acids 6-76 found in the whole natural molecule 1-76. According to Art. 10 (IX) of LPI, said analog is not considered an invention because it is part of the natural molecule, and accordingly is not patentable.

6.4.4 Sequence modifications

Modifications in protein sequences in order to differentiate them from natural sequences can be carried out in different way. Theoretically, any characteristic introduced into the sequence that was not described as naturally-occurring is acceptable as modification, for purposes of compliance with Art. 10 (IX) of LPI.

6.4.4.1 With natural amino acids (substitutions, insertions or deletions)

As highlighted above for modifications in general, modifications of biological sequences by inserting L-natural amino acids in the sequence (in the medium or at the ends) are considered sufficient for purposes of compliance with Art. 10 (IX), provided that the resulting sequence formed is not naturally-occurring either.
For deleting amino acids, the position of the deleted amino acid results in different situations to be considered. If it is located in the central part of the sequence of the protein, said modification is, theoretically, sufficient to differentiate it from the natural molecule. However, even if the deleted amino acids are contiguous and are at the end of the sequence, same still fails to

comply with Art. 10 (IX), since the resulting sequence continues to be identical to a part of the natural sequence (see example 32).
Regarding the substitution of amino acids by other natural amino acids, it is considered that said modification is sufficient for the sequence to comply with Art. 10 (IX), provided that there is no description of natural proteins in related species containing said substitution (see item 6.4.2 of orthologous proteins).
When analyzing proteins already described in the state of the art, care must be taken to evaluate the inventive step of the modification (insertion, deletion or substitution) made, taking into account the fact that some groups of amino acids present common properties. Thus, the inventiveness of these alterations in the protein sequence generally depends on the demonstration of an unexpected effect generated by the modification in relation to the state of the art.

6.4.4.2 With non-natural amino acids (including protector groups)
Insertions of amino acids which are not naturally-occurring (deriving from natural amino acids) are also considered sufficient modifications for the protein sequences to comply with Art. 10 (IX). Nevertheless, for purposes of clarity and precision, said amino acids shall be appropriately identified in the claims, so as to avoid the indirect inclusion of natural amino acids, and thereby result in the natural biological sequence.
The inclusion of such amino acids in the sequences presented in patent applications is also addressed in INPI Resolution PR N° 81/2013, cited in item 2.2.2 of these Guidelines; and a list with examples of non-natural amino acids and the acceptable abbreviations in the definition thereof is available in Table 4 of Appendix of this Resolution (published in the Official Federal Gazette (DOU) - Section 1, N° 68, April 10, 2013).

6.4.4.3 Grouping added to carboxyl or amino terminal
A protein sequence can also be altered by binding chemical groupings at their ends, these having the purpose of allowing anchorage to a certain surface or structure, increase of protein activity, modulation of bioavailability and/or circulating half-life, etc.
Once again, attention must be paid to the form in which said molecule is claimed, in order to guarantee the presence of the chemical grouping in said molecule, since it is this grouping that will differentiate it from its natural equivalent. Fmoc, t- boc, other chemical groupings, prosthetic groups, lipids, carbohydrates, iron, calcium, heme, are examples of groupings which when added to proteins may potentially differentiate them from natural ones.

6.4.5 Fusion proteins
By definition, these proteins are created by union (fusion) of parts of two or

more different protein sequences. Accordingly, a fusion protein involved in a patent application is formed by at least a "functional" portion, responsible for the property related to the invention.
Thus, for purposes of definition in accordance with Art. 25, it is important to underline that in a fusion protein, all the functional portions constituting the end protein must be described in the application.

6.4.5.1 Naturally-occurring

Rare cases of naturally expressed fusion proteins are noted in some types of cancer, owing to chromosome translocation, which may lead to the fusion of different genes, for example: fusion proteins gag-onc, Bcr-abl, and Tpr-met.
Once the occurrence of a natural identical structure is proven, with due regard for that prescribed in item 4.2.1 (for example, Bcr-abl, with a portion 1-50 of Bcr fusioned to the portion 13-78 of abl), such proteins cannot be considered inventions according to Art. 10 (IX) of LPI.

6.4.5.2 Characterization

In general, in defining fusion proteins, the rules defined for any other protein sequences apply (see item 6.4.1). Thus, no references are accepted for percentages of homology/similarity/identity, and the proteins shall be referred to by way of at least one of their sequences of amino acids or SEQ ID NO: corresponding to the functional portion.

6.4.5.3 Integral Seq ID

When the polypeptide sequence described in the patent application is claimed in the form of a fusion protein, it must always be at least by way of its sequence of amino acids or corresponding SEQ ID NO: for a clear and precise definition of the subject matter claimed relating to the invention.
When various peptides are related to the property described in the invention, and all are present in the fusion protein claimed, all these peptides shall be referred to at least by way of their sequence of amino acids or corresponding SEQ ID NO:.
Special attention must be paid to cases where the "fusion" protein is in fact formed by fragments of a same naturally-occurring protein: in accordance with the form as claimed, the end protein produced (fusion protein) may be an identical result to the natural molecule.

Example 33:

Claim: Fusion protein characterized by comprising:
a) a first polypeptide that consists of the sequence of amino acids 41-56 of SEQ ID NO: 2;
b) a first spacer of 6-27 amino acids;

c) a second polypeptide that consists of the sequence of amino acids 69-84 of SEQ ID NO: 2;
d) a second spacer of 5-11 amino acids; and
e) a third polypeptide that consists of the sequence of amino acids 92-105 of SEQ ID NO: 2.
In this claim, since the spacers of interest are not defined, said ranges being compatible with the interval between the sequences defined, the resulting "fusion" protein encompasses in its scope the very protein whose sequence is described in SEQ ID NO: 2, which is naturally-occurring, and so the claim does not comply with Art. 10 (IX).

6.4.5.4 Definition of just one of the sequences present in the fusion protein

When the protein of interest is fusioned to another other polypeptide that will solely act as "label/reporter", said reporter can be defined by way of its sequence of amino acids or corresponding SEQ ID NO:, as established previously, to any polypeptides. Nevertheless, since said polypeptide "reporter" is broadly known in the art, optionally the reference thereto can be made solely by way of its abbreviation, for example, to molecules such as GFP (green fluorescent protein), GST (glutathione S- transferase), CAT, c-Myc, FLAG, among others.
Potentially, an application may present the type of situation in which the inventive characteristic of the fusion protein is solely in the presence of the protein described in the application - which can also be the reporter portion - and it can be fusioned to various others.

Example 34:

The application describes a polypeptide X which, in isolation, has no surprising activity, but which is capable of enhancing the immunological response of antigens fusioned thereto. In the set of claims, there is claimed a "fusion protein characterized by consisting of protein X (defined by SEQ ID NO :) bound to an antigen".
In this case, attention must be paid to clarity and precision of the way in which the fusion protein is claimed, since the antigen fusioned thereto is not defined in the claim, and the decision to be taken shall consider the information available in the specification.

Situation 1: The specification presents examples of X fusion protein with various different antigens, not related, and demonstrates the indisputable efficiency of all the resulting proteins for the proposed purpose, so there is no indication that another antigen would not work in the same manner. In this case, it is not necessary to require that the application list all the possible antigens for use in the fusion protein, and it is considered that the claim as worded above is

acceptable.

Situation 2: the application presents examples of X fusion protein with various different antigens, not related, but the results demonstrated do not present consistency, demonstrating that the fusion protein is effective for some antigens and not for others. In this case, the very application does not provide full disclosure and basis in accordance with Arts. 24 and 25 to support that the fusion protein works with any antigen (it may include antigens for which there is no evidence that they work as described). Therefore, the set of claims shall be limited to the subject matter described and supported in the application in accordance with Arts. 24 and 25 of LPI, that is, the claims must specify which antigens of interest are present in the fusion protein claimed.

6.4.6 Antibodies

Antibodies are plasma proteins which bind specifically to substances known as antigens, and include polyclonals and monoclonals; therefore, they shall be analyzed as proteins, and also in terms of that prescribed in Art. 10 (IX) (see item 6.4 and subitems thereof).

Polyclonal antibodies are derived from different lineages of B cells. They are a mixture of immunoglobulin molecules secreted against a specific antigen, each recognizing a different epitope. These antibodies are biological products isolated from nature and, therefore, are not considered inventions according to that prescribed in Art. 10 (IX) of LPI. It must be underscored that the isolation of a specific antibody from this pool of antibodies does not exclude this molecule from compliance with Art. 10 (IX).

Monoclonal antibodies are antibodies from a single specificity, i.e. specific to a single epitope of an antigen. Through human intervention, a monoclonal antibody can be obtained by means of different techniques, such as hybridoma (see item 6.4.6.2) or genetic engineering.

Provided that it is obtained by hybridoma and characterized thereby, the monoclonal antibody cannot be considered natural and, therefore, complies with that prescribed in Art. 10 (IX). In this situation, this monoclonal antibody can be additionally defined by its specific sequence (SEQ ID NO:). In the case of monoclonal antibodies obtained by genetic engineering, they are defined by their sequence, and can be accepted provided that they comply with that prescribed in Art. 10 (IX) (see item 4.2.1).

Example 35:

Wording of antibody claim eligible for protection.

Claim: Monoclonal antibody against protein X characterized by the fact that it is produced by hybridoma HHH, deposited under number YYYY.

Example 36:

Unacceptable claims for antibodies.

Claim 1: Antibodies characterized by the fact that they are specific for protein X.

As the antibodies claimed are not clearly and precisely defined, these claims cannot be accepted since they do not comply with Art. 25 of LPI, and may encompass natural molecules, which is contrary to Art. 10 (IX).

Claim 2: Human monoclonal antibody characterized by the fact that it recognizes protein X and has an affinity of 2x10-9 M.

Claim 3: Monoclonal antibody and fragments thereof characterized by the fact that it is capable of binding to protein X.

As the antibodies claimed are not clearly and precisely defined, nor which fragments are being claimed, these claims cannot be accepted, since they do not comply with Art. 25 of LPI.

6.4.6.1 Process of obtaining antibodies

The process of producing a polyclonal antibody which consists solely of exposing an animal to an antigen, followed by purification, is considered a natural biological process, and is not considered invention, thus not complying with Art. 10 (IX). In some cases, however, when there is a non-trivial technical stage involving the determination of the epitope or modification of the antigen to elicit the immunological response, it is considered that there is significant human intervention, since it has a direct action on the molecule, which has a decisive impact on the end result obtained. In these cases, such processes are eligible for protection.

In contrast, owing to human intervention, the process of producing monoclonal antibodies is not considered a natural biological process, be it involving the obtainment of a hybridoma or by genetic engineering techniques.

Regarding the characterization of the process of obtaining antibodies, care must be taken for the need to define the stages of the process (see item 4.2.1.2).

6.4.6.2 Hybridomas

Hybridomas are the result of a fusion of two cell types, a myeloma with a lymphocyte B, and produce antibodies. They bear characteristics not achievable by such cell types under natural conditions, being the product of direct human intervention. According to the understanding adopted by this Institute, technically speaking, a hybridoma is considered a transgenic microorganism, and accordingly, said subject matter is patentable because it complies with Arts. 10 and 18 of LPI.

At the same time, since this concerns biological material essential for the practical realization of the object of the patent application, and cannot be

characterized clearly and precisely in the specification, in order to comply with the sole paragraph of Art. 24 of LPI, it is essential to deposit the hybridoma by the filing date of the patent application or its priority date, and the submission of the deposit number in the patent application (see item 2.2.1).

6.4.6.3 Chimeric/humanized antibodies

When the monoclonal antibodies of mice, rabbits, etc., are used as therapeutic agents in humans, the strange proteins are recognized by the immune system of the human host. The advent of chimeric/humanized antibodies is a mechanism used to solve this therapeutic obstacle.

The technology for producing a humanized antibody differs from the production of a monoclonal antibody because it does not depend on cultivating the hybrid cell, but implies obtaining the sequence of the immunoglobulin (human Fc portion and variable portion of the non-human Fab fragment). These sequences are merged and placed in an expression vector for subsequent cultivation of the transfected host cell and subsequent stages of purification. Owing to this difference in the production route, the characterization of humanized antibody requires the presentation of a SEQ ID NO: X containing a sequence of amino acids of the variable portion of the antibody and the definition of the other elements (Fc portion).

Example 37:

Wording of antibody claims eligible for protection.

Claim: Humanized antibody against α-actin characterized by comprising the murine variable region which consists of SEQ ID NO: X and human γ chain regions.

Claim: Humanized antibody againstα-actin characterized by comprising the murine complementarity determining regions (CDR1; CDR2; CDR3) which consist of SEQ ID NO: X, SEQ ID NO: Y and SEQ ID NO: Z in the light chain and SEQ ID NO: A, SEQ ID NO: B and SEQ ID NO: C in the heavy chain and human γ chain regions.

6.4.6.4 Fragments of antibodies

An antibody molecule can be cleaved generating different fragments with distinct functions. If originating from antibodies found in nature, or are part of other natural proteins, the fragments in themselves are not patentable owing to Art. 10 (IX) of LPI (see item 6.4.3).

Modifications of antibody fragments may also constitute subject matter eligible for protection, as in the case of single-chain variable fragments (ScFv). The Fv fragments are not covalently connected, so the heterodimers of the VH and VL domains can easily dissociate. However, Fv fragments can be constructed so as not to dissociate, that is, the VH and VL domains can be joined by a connector, creating a single-chain FV fragment. Despite being an antibody fragment, this construction complies with Art. 10 (IX) of LPI, since these fragments are not

found in nature joined by the connector.

7 Animals, plants, parts thereof and processes of obtaining them

7.1 Animals, plants and parts thereof

If natural/isolated, these are not considered an invention, according to Art. 10 (IX). When resulting from genetic manipulation by the human being, they are not patentable, according to Art. 18 (III).

7.1.1 Products and processes involving stem cells

Stem cells are undifferentiated cells (totipotent, pluripotent or progenitor) which can be stimulated to specialize in the tissues that make up the human body. According to these Guidelines, products and processes involving stem cells refer exclusively to pluripotent or progenitor stem cells. These cells can be obtained directly from various tissues of the adult organism (such as, for example, from bone marrow, from adipose tissue), or even from the umbilical cord, or can be obtained by de-specializing a specialized adult cell (as in the case of the induced pluripotent stem cell – IPS).

Alternatively, they can be obtained from the internal mass of the blastocysts originating from human embryos produced by in vitro fertilization, according to the provisions of Art. 5 of the Biosafety Act – N°. 11,105/2005.

In accordance with LPI, the cells themselves obtained directly from an animal or with some gene modification, are not patentable in light of that prescribed in Art. 10 (IX) or 18 (III), respectively. Nevertheless, compositions containing these cells, the processes of obtaining stem cells and applications (uses) thereof can be considered patentable provided that they do not imply or include a therapeutic and/or surgical method (Art. 10 (VIII), and provided that they comply with the provisions of Art. 18 (I) of LPI.

For example, the following products and processes involving stem cells can be considered eligible for patenting:

- Compositions containing cells and other ingredients (various implants containing cells, cell and matrix formulation, cells and growth factors ...).
- Composition containing mixtures of different types of stem cells.
- Processes of purification, preparation, conditioning, specialization, despecialization, or any processing of stem cells provided that it is performed in vitro.
- Uses of cells for preparing medicines to treat disease X.
- Uses of cells for preparing implants to treat disease X.
- Uses of cells for preparing compositions for diagnosing disease X.
- Processes of diagnosis which include stages that employ cells or synthetic tissues, provided that they are performed in vitro.
- Drug tests which include stages that employ stem cells or synthetic tissues, provided that they are performed in vitro.

• Processes of cultivating stem cells.
• Conditioned culture media obtained during the cultivation of stem cells.

7.2 Transgenic plants, parts thereof and processes of obtaining them

These are plants that had their genome modified by the introduction of a DNA manipulated by recombinant DNA techniques, and whose modification would not occur under natural conditions of cross-breeding or recombination.

Transgenic plants and parts thereof (for example, transgenic cell, tissue transgenic and transgenic organs) are not considered to be patentable subject matters according to Art. 18 (III and sole paragraph) of LPI.

Even if the process of obtaining transgenic plants is patentable, it is important to emphasize that the intermediary and/or end products of this process, that is, the transgenic plant and/or parts of this plant constitute subject matters expressly prohibited from patentability according to Art. 18 (III and sole paragraph) of LPI. Nevertheless, there is no restriction on the patenting of the processes of obtaining these plants.

Examples of claims eligible for protection

• Method of producing a transgenic plant characterized by the fact that it comprises the stages of:

(a) obtaining an explant from the plant;

(b) exposing the explant to the Agrobacterium tumefaciens culture that contains the vector defined by claim X (duly described with a selection gene, a heterologous gene and the sequence promoter(s);

(c) cultivation of the explant in a medium with the specific conditions for cultivating a vegetable tissue; and

(d) selecting and cultivating transformed calluses that express the heterologous gene, to induce the formation of the embryonic callus.

• Method for producing a transgenic dicotyledonous plant, characterized by comprising:

(a) transforming plant cells using an Agrobacterium transformation vector that comprises a chimeric genic construction Y;

(b) obtaining a transformed plant cell; and

(c) regenerating a genetically-transformed plant from the transformed plant cell.

7.3 Process of obtaining plants by cross-breeding

Article 10 (IX) of LPI establishes that natural biological processes are not considered inventions, and therefore excludes patenting of natural biological processes, including those for producing plants.

A "natural biological process" is understood to be any process that does not use technical means to obtain biological products or that, even using a technical

means, it would be eligible for occurring in nature without human intervention, consisting wholly of natural phenomena. In this sense, biological processes are considered non- natural when human intervention is direct in the genetic composition and are permanent in character.
Thus, processes involving the cross-breeding of plants genetically-modified by direct human intervention are eligible for protection.

Example 38:
Non-transgenic parenting.
Claim 1: Method for producing a plant of X characterized by comprising the stages of:
a) selecting a plant of X homozygote for the gene A;
b) selecting a plant of X homozygote for the gene B; and
c) cross-breeding the plants selected in stages (a) and (b) for producing a hybrid plant.
Conventional methods of producing plants based on stages of selection, cross-breeding and propagation are considered natural biological processes, and do not comply with Art. 10 (IX). In these cases, human interference by way of selection and induction of specific cross-breeding is not essential for the process to occur, solely accelerating or limiting that which would occur in nature.

Example 39:
Non-transgenic parenting.
Claim 1: Method for producing a plant of X with high levels of compounds W characterized by comprising the stages of:
a) identifying the gene markers connected to high levels of W;
b) selecting the individuals comprising the markers identified in stage (a); and
c) cross-breeding the individuals selected in stage (b).
Conventional methods of producing plants based on stages of selection, crossbreeding and propagation in which human intervention consists solely of providing additional technical means to facilitate or direct the process – in this case, the identification of gene markers – are considered natural biological processes, not complying with Art. 10 (IX). In these cases, human interference is not decisive in order to obtain the end result, merely accelerating or limiting that which would occur naturally.

Example 40:
Transgenic parenting.
Claim 1: Method of producing hybrid seeds characterized by comprising the cross-breeding of a herbicide-resistant plant with a plant endowed with an enhanced nutritional value comprising in its genome a heterologous gene encoding a modified

albumin.

Claim 2: Method of introducing the characteristic of resistance to a herbicide in a plant endowed with enhanced nutritional value characterized by comprising the stages of:

a) cross-breeding a plant resistant to at least one herbicide with a plant comprising in its genome a heterologous gene encoding a modified albumin;

b) developing base populations;

c) evaluating the plants obtained individually; and

d) selecting plants endowed with enhanced nutritional value comprising the characteristic of herbicide resistance.

This process involves the technical stage that is essential for obtaining plants that do not occur in nature and, therefore, complies with Art. 10 (IX).

8 Patent applications involving components from the Brazilian genetic heritage

Patent of invention applications for a process or product obtained from a sample of components of the Brazilian genetic heritage, deposited as of June 30, 2000, shall adhere to the rules in effect, as established in MP 2186-16/01 dated August 23, 2001, as well as CGEN Resolution N° 34 dated February 12, 2009 and INPI PR N° 69/2013, dated March 18, 2013.

MP 2186-16/01 provides, among other things, on property, rights and obligations relating to access to components from the Brazilian genetic heritage existing in national territory, on the continental shelf and in the exclusive economic zone for purposes of scientific research, technological development or bioprospecting, as well as access to traditional knowledge associated to the genetic heritage, relevant to the conservation of biological diversity, to the integrity of the country's genetic heritage and to the use of components thereof (Art. 1, items I and II).

In Art. 31, the provisional presidential decree determines that the grant of the industrial property right over a process or product obtained from a sample of a component of the genetic heritage requires compliance with the Provisional Presidential Decree (MP), and the applicant shall inform the origin of the genetic material and the associated traditional knowledge, as applicable.

The rules established in Provisional Presidential Decree (MP) 2186-16/01 shall be adhered to for patent applications involving genetic heritage. Non-exhaustive examples include organisms (plants, animals, fungi, bacteria, archaea, etc.), parts of organisms (leaves, nails, skin, mucus, blood, roots, extracts, organs, oils, venoms, fangs, etc.), molecules isolated from organisms (DNA, RNA, proteins, sugars, lipids, etc.), and their synthetic correspondents, as well as compositions and processes containing any of the items mentioned above. In accordance with Art. 3, the MP does not apply to human genetic heritage.

The applicant shall always furnish information relating to the origin of the material through petitions established in INPI Resolution PR N° 69/2013: a petition for access information or a petition of declaration that the application filed does not involve access under the terms of MP 2186-16/01. Pursuant to CGEN Resolution N° 35/2011, for purpose of regularization, the request protocol for authorization to access a genetic resource may be accepted, and the allowance of the patent application shall require presentation of the definitive authorization to access the genetic resource.

9 References (OMIT)