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Examination Guidelines for Patent Applications

The Biotechnology Field

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Summary

Ministry of Economy
National Institute of Industrial Property
Board of Directors of Patent, Computer Programs and Integrated Circuit Topographies

EXAMINATION GUIDELINES FOR PATENT APPLICATIONS IN THE BIOTECHNOLOGY FIELD

This text will be an integral part of the Examination Guidelines for Patent applications and aims to setting out the current understanding of the BRPTO on Biotechnology Inventions. Other inherent examination topics are listed and discusses in said general guidelines.

Patent Division – April, 2020

1 Biotechnology protection requirements

[1] The requirements of novelty and inventive step are discussed in the Examination Guidelines for Patent Applications, Block II. This Annex will highlight only some specific characteristics of biotechnology patent applications.

1.1 Industrial application

[2] The concept of industrial application in the biotechnology field must comply with the matters set forth in the Examination Guidelines for Patent Applications (Block II), and special attention must be paid to the definition of utility for the claimed invention.

[3] When the invention involves biological sequences, the industrial application requirement is met only when some utility is disclosed by said sequence.

[4] Thus, if a patent application identifies a new sequence through homology, with the homologous sequence described in the state of the art having a known function, the new sequence identified in the patent application is liable of 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 there is no known biological function for this protein in the state of the art. It is ascertained that this protein described in the application is an important marker for the diagnostic of prostate cancer.

Inventions related to this protein (for example, use, composition, diagnostic kit) are suitable for industrial purposes, as the application clearly discloses a p ractical use for the sequence (marker for the in vitro diagnosis of prostate cancer), even if its biological function is unknown.

Example 2:

The application discloses the protein of SEQ ID NO: 1 that was isolated from yeast, but it does not disclose any function/ application for the protein which does not present any homology with a protein whose function is known.

The specification presents a merely speculative list of applications without technical grounds able to provide solid support for any practical application of the protein. This protein and/ or its use and/ or the compositions comprising it, are not suitable for industrial application, as these materials do not present any defined practical utility.

2 Conditions for patent protection in biotechnology

2.1 Unit of invention

[5] A patent application must refer to a single invention or to a group of interrelated inventions as to comprise a general single inventive concept (article 22 the Brazilian IP Statute – Statute #9,279/96; see Examination Guidelines for 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 the SEQ ID NO: 1, 2, or 3.

The specification mentions that the three nucleic acids encode dehydrogenases that include a conserved motif sequence which defines 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 the nucleotide and amino acid sequences.

The same technical or equivalent characteristics that are shared among the nucleic acid molecules are in their common properties (coding dehydrogenases) and their shared structural elements that are essential for their common property (the conserved motif). Consequently, there is a special technical characteristic and SEQ ID NOs: 1, 2, and 3 are endowed with unity of invention.

2.2 Sufficiency of disclosure (article 24 of the Brazilian IP Statute)

[6] Article 24 of the Brazilian IP Statute establishes that the specification must describe the subject matter clearly and sufficiently so as to enable a person skilled in the art to carry it out. It is understood that subject matter means the matter for which protection is sought, meaning the matter contained in the claim chart. Consequently, the analysis of the sufficiency of disclosure of the claimed subject matter must be assessed on the basis of what was disclosed in the specification, sequence listing and drawings (if any).

[7] It must be ensured that the application contains sufficient technical information to allow a person skilled in the art to put the invention into practice, without undue experimentation (see item 2.15 of the Examination Guidelines for Patent Applications, Block I).

[8] In the biotechnology area, it is understood that it is tolerable to carry out standardization experiments for the person skilled in the art to reproduce the invention,

and these would not constitute undue experimentation. In this sense, it is not considered undue to carry out experiments that are obvious and/ or routine for a person skilled in the art at the time of the filing, even if such experimentation is laborious and/ or tedious (e.g. the standardization of the optimal conditions for the PCR reaction, when the technical problem solved by the invention does not lie in the specific adjustment of these conditions).

[9] When the application refers to a product or process involving a biological material that might not be described in a manner whereby a person skilled in the art can understand and reproduce the matter, the specification must be supplemented by the filing of the above-mentioned material (see item 2.2.1).

[10] Two examples of insufficiency of disclosure in the Biotechnology Area warrant special mention. The first is when the embodiment of the invention depends upon chance. In this situation, even if a skilled technician follows the instructions given in the application, there is no guarantee of obtaining the alleged results. These cases must be questioned, pursuant to the provisions set forth in article 24 of the Brazilian IP Statute (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 that includes the amplification of a specific DNA sequence through the use of a specific pair of primers, in which these primers are not complementary to any part of the DNA sequence, which would make the execution of the method unfeasible.

Example 4:

The application describes a mutant microorganism obtained through random mutagenesis with UV radiation. As obtaining the microorganism is dependent on random chance, the sufficiency of disclosure of the microorganism will be complied only by filing the microorganism (see item 2.2.1.1). The document proving the filing of the microorganism in question may be presented through clarifications during the technical examination, provided that the filing of the microorganism occurred up to the filing date of the application (or the priority date of the application, if any). The microorganism obtained through UV-induced mutation and filed in this manner will not fall under article 10 (IX) provided that there is no evidence that a microorganism with said characteristic is found in nature.

Example 5:

The application describes a new and inventive method for obtaining mutant microorganisms through random mutagenesis. As the steps of the above-mentioned method are described in detail in the specification, it is possible for a person skilled in the art to reproduce the invention. Consequently, such method presents

sufficiency of disclosure, complying with the provisions set forth in article 24 of the Brazilian IP Statute. Should this method be related to obtaining only a single mutant with specific characteristics, the information of the filing thereof must be set forth in the claim, as there is no guarantee of obtaining the same result.

Example 6:

The application describes a method that uses a mutant microorganism. The specification does not provide details on the process of obtaining the microorganism, but characterizes it through its respective filing number. In this case, it is considered that the person skilled in the art could reproduce the method in question using the filed microorganism. Thus, the invention complies with the sufficiency of disclosure condition.

Example 7:

The specification discloses a protein through its NCBI-sequence database access number or through reference to a scientific paper, with this protein being essential for the embodiment of the invention. In order to comply with the sufficiency of disclosure requirement set forth in article 24 of the Brazilian IP Statute, the applicant is required to include the sequence in question in the application, as disclosed in the database at the time of filing/ priority date, presented as a sequence listing, without this resulting in the inclusion of additional matter, as such protein may be identified quite clearly through its access number or the above-mentioned scientific paper (see additionally items 2.2.1.1 and 2.2.2).

Example 8:

The application describes a new dopaminergic receptor duly characterized through its amino acid sequence. The application mentions that the antagonists and agonists of the receptor are also useful. However, the application does not provide a technical description of any of the receptor's antagonist and agonist compounds. The person skilled in the art would not be able to implement the invention related to the antagonists and agonists due to the lack of technical instructions on how to do so, as the mere description of a receptor does not provide sufficient information on the molecules that could stimulate or inhibit its functioning. Thus, it is understood that the subject matters related to the enzyme antagonists or agonists do not comply with the sufficiency of disclosure condition (see also item 3.1).

2.2.1 Deposit of biological material

[11] Should biological material be essential for the practical implementation of the object of the application, which cannot be described in compliance with article 24 and when not accessible to the public, the specification shall be supplemented by filing the material at an institution authorized by the BRPTO or indicated under an international agreement in force in the country, or in any of the international deposit authorities recognized by the Budapest Treaty1 (see item 2.18 of the Examination Guidelines for Patent Applications, Block I), as per the sole paragraph of said article. Thus, it is considered that "biological material", in this context of the deposit, can refer to any material containing genetic information and capable of exercising direct or indirect self- replication. Representative examples include bacteria, archaea, protozoa, viruses, fungus, algae, seeds, animal and plant cell lines, hybridomas, artificial chromosomes and other vectors; in some of these cases and depending on the requirements of the selected filing center, the host cell containing these biological materials may be filed.

2.2.1.1 Cases in which biological material must be deposited

[12] It is important to stress that, as mentioned above, the Brazilian IP Statute refers to the filing of biological material that might not be described as set forth in article 24, meaning that it might not be described in a clear and sufficient manner in the specification. It is thus concluded that the deposit of the material does not necessarily apply to all and any biological material involved in a specific invention, since, for example, polynucleotides and polypeptides, must be described through theirnucleotide

1 For a list of signatory countries of the Treaty of Budapest, see http://www.wipo.int/treaties/en/ShowResults.jsp?lang=en&treaty_id=7.

For a list of international deposit authorities (IDAs), see http://www.wipo.int/export/sites/www/treaties/en/registration/budapest/pdf/idalist.pdf.

and amino acid sequences (note: nevertheless, there is nothing that prevents such materials to be additionally deposited).

[13] With regard to microorganisms with nucleotide sequences different from those found in nature, the application must present the modified nucleotide sequence through the sequence listing (see item 2.2.2), or its denomination as known at the art, or the microorganism deposit data. When essential for ascertaining inventive characteristics, specific promoters, the place of insertion in the genome of the heterologous material, the methodology for obtaining the sample, among other essential characteristics, must also be present in the specification, in order to allow a person skilled in the art to implement the invention.

[14] In cases where the microorganisms are selected through random mutagenesis and the genetic alterations that result in an outstanding effect are not defined in the application, in order to comply with article 24 of the Brazilian IP Statute, the microorganism must have been filed with an international deposit authority, and the deposit data (such as deposit declaration or name of the institution, with the number and date of the deposit) form part of the application (see item 2.2.1). In this sense, the biological material will be available at the deposit authority and shall consequently be considered as being clearly and sufficiently described, as well as replicable. Should the microorganism not have been deposited, the subject matter will not be in accordance with article 24 of the Brazilian IP Statute.

[15] When the inventive characteristic obtained through genetic alteration is achieved only with a specific strain used in the application under examination, it is considered that the microorganism per se is essential for the implementation of the invention and it is consequently necessary to deposit the biological material in order to ensure that the subject matter complies with article 24 of the Brazilian IP Statute. On the other hand, it is not necessary to deposit the biological material when the inventive characteristic might be achieved with several available strains or species of microorganisms using the methodology described in the application. Thus, for situations in which widely known organisms are merely transformed in order to express a new and surprising characteristic, it is sufficient to indicate the organism of interest, relating it specifically to the nucleic acid to be used in such transformation, and ensuring that such nucleic acid is described in a clear and accurate manner.

[16] In cases wherein the invention does not lie in a microorganism or a biological material per se, but its use, modification or culture thereof, and a person skilled in the art is unable to perform the invention without having the sample mentioned in the application, the deposit of the microorganism or the biological material is also mandatory.

2.2.1.2 Deadlines for depositing biological material

[17] With regard to the original deposit of biological material for patent purposes, items

2.17 and 2.18 of the Examination Guidelines for Patent Applications, Block I, establish that the deposit of biological material must be carried out until the filing date of the patent application, and that such data must be included in the specification. Should there be a Union priority, the deposit of biological material must be carried out prior to or by the priority date claimed, if pertinent, in other words, if the priority rights are applicable to the biological material.

[18] When the evidentiary data on the deposit of the biological material are not presented in the patent application, and the patent examiner deems such data necessary, a technical requirement must be issued for the applicant to reply. Should such requirement not be complied with, the application must be rejected, grounded on article 24 of the Brazilian IP Statute.

2.2.2 Sufficiency of disclosure of the sequence listing

[19] The patent application whose subject matter contains one or more nucleotide and/ or amino acid

sequences that are crucial for the description of the invention shall contain a sequence listing section in order to comply with the sufficiency of disclosure addressed in article 24 of the Brazilian IP Statute (see Examination Guidelines for Patent Applications, Block I). It is noted that, should the application use and refer to sequences known in the art and should they be necessary for the embodiment of the invention, the patent examiner may issue a requirement requesting the presentation of the sequences. It must also be noted that the sequences must correspond to those known as the state of the art at the time of the filing/ priority date (i.e. as disclosed in the data bases), taking into account possible refinements or alterations in the sequences over time.

[20] In the case of degenerate nucleotide sequences, they can be accepted, as long as they generate the same protein (see item 6.1, § [68]), without the need to present each of the possibilities of nucleotide sequences in the sequence listing section.

[21] According to article 41 of Normative Instruction 31/2013, the sequence listing must be submitted to the Brazilian PTO in accordance with the Rules in force. Currently, the Rules that deals with the presentation of sequences is Rule PR # 187/2017.

2.3 Support, clarity and precision (article 25 of the Brazilian IP Statute)

2.3.1 Support in the specification

[22] The subject matter for which protection is sought must be duly supported in the specification. To do so, the description presented through the specification must provide technical information able to provide solid support for all the claimed subject matter.

Example 9:

Claim 1: Immunogenic protein characterized by consisting of SEQ ID:1, and its fragments.

The specification presents a mutated immunogenic protein (not natural) of 600 amino acid residues and also discloses an immunogenic fragment of such mutated protein (not natural), determined as consisting of residues 320 to 400 of the said protein. The claim chart claims protection for the immunogenic protein and for the immunogenic fragments of this protein (claim 1). However, the specification discloses only an immunogenic fragment of said protein, namely: the one that begins at position 320 and ends at position 400 of the protein. In this case, as the patentability requirements set forth in article 8 of the Brazilian IP Statute have been complied with, a requirement must be issued on the basis of articles 24 and 25 of the Brazilian IP Statute, whereby the claimed subject matter shall be limited to only that sufficiently described and effectively supported by the specification, which is an immunogenic protein and its fragment which comprises the residues 320 to 400 of said protein.

In this example, even if the applicant presents new information on other immunogenic fragments of the said protein that have not been described in the subject matter initially disclosed, such information may not be taken into consideration, as the specification did not mention other immunogenic fragments of said protein different than that comprised between the amino acids 320 and 400 of the protein. Consequently, the fact remains that the claim for broad-ranging protection of “immunogenic protein fragments” may not be accepted due to the absence of sufficiency of disclosure and adequate support for the subject matter in the specification.

Example 10:

Claim 1: Process for transforming a plant characterized by the introduction of the gene X into 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 such process would not be applicable in the same manner to both groups of plants, and consequently the claim including

gymnosperms would not be supported by sufficient information in the specification. This lack of support could be overcome through evidence that the transformation of gymnosperms could be carried out under the same conditions already mentioned for angiosperms.

However, should the data supplied in order to present sufficient support for the gymnosperm claim, introduce new parameters or any non-trivial adaptations for a person skilled in the art, such information may not be accepted. This is because data must be included in the specification, which would constitute an addition of subject matter, thus not complying with article 32 of the Brazilian IP Statute.

3 Claims

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

[24] In the biotechnology area, some non-exhaustive examples of subject matter considered to fall into the "products" category are: nucleic acids, peptides, polypeptides, proteins, microorganisms, virus, cells, vectors, plants, seeds, hybridomas, antibodies, probes, vaccine 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 nucleic acid/ polypeptides/ peptides sequence; process for producing a transgenic microorganism/ plant/ animal; purification method; processes for extraction/ isolation, among others.

3.1 Reach-through claims in biotechnology

[25] The reach-through claim is a special type of claim that is designed to provide protection for future inventions based on a current invention. In other words, this type of claim is intended to provide protection for inventions that have not been identified by the inventor by the filing date of the patent application, but that might be identified in the future through the use of the actual invention

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

[27] Reach-through products (drugs, agonists, antagonists, etc.) are usually identified only by reference to a material or method used in the identification thereof, without defining their chemical structures. Alternatively, these products are defined in terms of a function associated with the actual invention, as this is the only information available to the inventor. Consequently, both the compounds that are already known from the state of the art as well as those that are still to be identified are encompassed by the scope of the claim, which thus becomes quite broad-ranging.

[28] Another type of reach-through claim in biotechnology is the process for identification of modulating compound claim. For this type of claim, the compound identified by the process is not defined through its structure but rather by its capacity to modulate the expression of a protein or gene involved in a disease, for example, or the screening method that is used to identify said compound. The common characteristic for these types of claims is that the material to be protected is not known.

3.1.1 Technical examination of reach-through claims

[29] The subject matter addressed by reach-through claims typically do not present sufficiency of disclosure, clarity, accuracy and/ or support, thus not complying with articles 24 and 25 of the Brazilian IP Statute.

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 polypeptide X as identified through the process defined in claim 1.

The application refers to a new and inventive screening process for modulators of activity of a polypeptide already known in the state of the art (polypeptide X), whose activity was demonstrated as being involved with disease Y, although without characterizing the compounds identified by said process.

Claim 1 defines the main invention of the application, which is a method of screening compounds of therapeutic interest and that modulate the activity of polypeptide X, which constitutes the actual invention, while claim 2 is a reach-through type that, in this situation, may include in its scope compounds that are already known and not modified in any manner whatsoever by the process used in their identification, as well as compounds that are not yet known.

Although the application describes the screening process specified in claim 1 in a sufficient manner, and may thus be accepted for this aspect, claim 2 is not accepted due to the lack of sufficiency of disclosure (article 24 of the Brazilian IP Statute), clarity, accuracy and support (article 25 of the Brazilian IP Statute). Claim 2 uses functional (rather than structural) characteristics to define the subject matter for which protection is claimed. However, the definition of a product through functional characteristics frequently results in a lack of clarity for the subject matter. A person skilled in the art would not be able to implement the definition of the claimed subject matter, because the compounds claimed per se (claim 2) offer potentially unlimited structural possibilities, thus including compounds that are still to be identified and/ or that are already available in the state of the art and/ or that are encompassed by the prohibitions set forth in article 10 (IX) of the Brazilian IP Statute.

Claim 2 claims protection for candidate compounds identified through the screening method of the invention as defined in claim 1.

These compounds were technically defined only by their activity (that is, a functional definition – wording that is common to 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; such situation would force said person skilled in the art to test countless compounds that are already known as well as all compounds that could be identified in the future using the screening method of the invention, in order to determine which of the compounds would have the desired activity and would thus be encompassed by the scope of the claims under examination.

4 subject matters excluded from protection according to the Brazilian IP Statute

4.1 Definitions

[30] Pursuant to the understanding adopted by this Institute, from the technical standpoint, the terms and expressions used in articles 10 and 18 of the Brazilian IP Statute are construed in the following manner:

- 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” encompasses 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 thereof, as well as any substance produced through biological systems, such as hormones and other secreted molecules, viruses or prions. It is worth stressing that synthetic molecules that are identical to or indistinguishable from their natural counterparts are also encompassed by this definition;

- "isolated from nature" is understood as all and any material extracted and subjected to an isolation or purification process, i.e. that removes it from the natural context;
- "genome" is the set of genetic information of a cell, organism or virus;
- "germplasm" is the set of hereditary material of a representative sample of individuals belonging to the same species;
- "natural biological process" is any biological process occurring spontaneously in nature and where human intervention does not affect the final outcome;
- "therapy" is a method of treatment aimed at curing or preventing a disease or faulty functioning of the body;
- "surgery" is defined by the nature of the treatment instead of its purpose, meaning regardless of whether the manual or instrumental intervention in the patient's body is undertaken for aesthetic or therapeutic purposes; and
- "diagnosis" refers to the identification of a specific disease; and
- "human or animal body" includes from the embryo to adult forms, i.e. it encompasses all stages of development.

4.2 subject matters not considered as inventions (article 10 of the Brazilian IP Statute)

4.2.1 natural biological products and processes (article 10 (ix) of the Brazilian IP Statute)

[31] With regard to claims in the "product" category, article 10 (IX) of the Brazilian IP Statute stablishes that it is not considered invention the whole or part of natural living beings and biological material when found in nature, or isolated therefrom, including the genome or germplasm of any natural living being.

[32] For claims in the "process" category, such as processes, methods, uses, applications, among others, article 10 (IX) of the Brazilian IP Statute refers solely to natural biological processes, ruling that they are not considered inventions.

[33] As article 10 (IX) of the Brazilian IP Statute stipulates that the whole or part of natural living beings and biological materials found in nature that are not deemed to constitute inventions, documents published subsequent to the priority/ filing date of the application under analysis may be used, in order to prove that the claimed subject matter falls under the provisions set forth in article 10 (IX) of the Brazilian IP Statute, provided that the information submitted clearly proves, without a shadow of doubt, the existence in nature of the claimed subject matter.

4.2.1.1 Natural biological products

[34] The whole or part of natural living beings and biological materials found in nature

– even if isolated therefrom or produced in a synthetic manner that have natural counterparts occurring in nature with no way of distinguishing them from their natural counterparts –, are considered as natural biological products and shall not be deemed to constitute inventions, as they are fall under the provisions set forth in article 10 (IX) of the Brazilian IP Statute.

[35] Thus, the inclusion of a disclaimer with the expression "not natural" does not overcome, in itself, the objection raised grounded on article 10 (IX) of the Brazilian IP Statute.

4.2.1.1.1Compositions containing natural biological products

[36] A composition claim whose sole characteristic is the presence of a specific product also confers protection on this product per se. Thus, a composition claim that is characterized only by containing a non-patentable product (for example, a natural extract), might not be granted, as this would protect the non-patentable product itself.

That is, with more grounds herein than for patentable components, such claims require parameters or characteristics that clearly determine, without a shadow of doubt, that this is an actual composition.

[37] In these cases, special care must be taken with the wording of the claim in terms of the other component(s) of the composition in question, in order to avoid that it ultimately represents a mere dilution (an aqueous solution, for example) of the non- patentable product. Bearing in mind that the purpose of a composition is to place the active component(s) in an appropriate manner to the purpose for which it/ they is/ are intended, a "mere dilution" would consist of the solvent not contributing to this final purpose, being merely the means used for the extraction. Therefore, it is possible that a water-based or ether-based extract from a specific plant, for example, although containing a component (extraction solvent) in addition to the extract itself, does not represent a composition ready for use in terms of its final purpose, and this same diluted extract in some other solvent (for example, used to make the active ingredient absorbable) represents a de facto composition, rather than a "mere dilution".

4.2.1.1.2Extracts

[38] Extracts are biological materials isolated from nature and, therefore, are not considered an invention based on article 10 (IX) of the Brazilian IP Statute.

[39] Thus, for compositions containing extracts, the same considerations pointed out above for natural products apply.

4.2.1.1.3Enriched extracts

[40] Extracts that differ from their natural counterparts for being enriched by some of their components are liable to protection only when presenting in their composition characteristics that cannot be attained normally by the species and that arise from direct human intervention.

[41] Attention must also be paid to the issue of extracts of transgenic bacteria cells. Although the microorganism per se might be patentable, it might not always apply to its extract, as cases might occur where it is not possible to distinguish the transgenic cell extract from the wild extract (for example, when the transgenic microorganism merely super expresses an endogenous protein).

Example 12:

Claim: Plant extract characterized by being enriched with isoflavones.

The extract is enriched with isoflavones by the isolation method. In this case, it is considered that the modification of such extract is the result of the simple fractioning of a natural extract isolated from nature, and this claim, consequently, falls under article 10 (IX) of the Brazilian IP Statute.

Example 13:

Extract enriched through to genetic manipulation.

Claim: Enriched plant extract characterized by comprising human insulin.

The application describes a process of alteration in the composition of the plant extract through expression of the human insulin gene, resulting in an enriched extract. In this case, it is considered that the modification of such extract is the result of genetic manipulation of the organism from which it is extracted. Thus, as this material is obtained from plants presenting characteristics that cannot be normally attained by the species, arising from direct human intervention, such extract is open to protection.

4.2.1.2 Natural biological processes

[42] "Natural biological process" is understood by any biological process occurring spontaneously in nature and where human intervention does not affect the final outcome.

[43] If the technical intervention plays an important role in determining the outcome or should its influence be decisive, the process is considered as an invention. That is, the processes that contain at least one technical step with a decisive impact on the final outcome and that might not be achieved without human intervention, are considered to constitute inventions.

[44] Regarding this concept, the classic process of obtaining plants or animals is not an invention. Similarly, processes that encompass only steps of mimetizing events that occur in nature are also not considered to constitute inventions. In contrast, methods based on genetic engineering (for example, the production of a transgenic plant), wherein the technical intervention is significant, are liable of patent protection.

[45] Microbiological processes encompass processes that use, are applied to, or result in microorganisms. Although these processes are biological processes, the BRPTO considers that they are allowable as they constitute an exception to the legal exclusions permitted in the TRIPS Agreement (Article 27 (3b)).

[46] Similarly, the BRPTO considers that biological or enzyme-based processes for obtaining chemical compounds are liable of patent protection when presenting a technical step that is decisive for the final outcome.

[47] Like other processes, claims of correctly formulated biological processes define the starting material, the product obtained and the means of transforming the former into the latter; the various steps necessary to achieve the proposed objective; or in the use case, the material to be used and the purpose of the use.

[48] Examples of suitable claims (note: the level of detail required will depend on the specific invention being examined):

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

4.2.1.3 Use of natural products

[49] When the claimed process involves the whole or part of natural living beingsand biological materials found in nature, including the genome or germplasm, but it does not consist of a natural biological process, there is no impediment hampering its patentability under the provisions set forth in article 10 (IX) of the Brazilian IP Statute. Thus, the use of a natural product might be liable of patent protection, provided that it complies with the patentability requirements.

Example 14:

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

Claims related to the use of natural resin for the preparation of cosmetic compositions may be accepted, when compliance with patentability requirement is ascertained, as there is no article in the Brazilian IP Statute preventing the use of natural products in activities that do not constitute natural biological processes.

Example 15:

Claim: Use of RNAse characterized by being in the cleavage of the RNA.

Use of natural material for performing its specific natural function is not considered to constitute an invention under article 10 (IX), as it consists of a natural biological process.

4.3 Non-patentable inventions (article 18 of the Brazilian IP Statute)

4.3.1 Non-patentable inventions as they fall under article 18 (i) of the Brazilian IP Statute

[50] Pursuant to article 18 (I), "that which is contrary to morals, good customs and public security, order and health" are not patentable.

[51] As biotechnology is a technological field generating inventions that involve matters that could raise moral issues and matters of public order, the current doctrine allows the BRPTO to reject to patent such inventions, grounded on article 18 (I) of the Brazilian IP Statute.

[52] The following examples are non-exhaustive:

(a) human cloning processes;

(b) processes of modification of the human genome that cause the modification of the genetic identity of human germ cells; and

(c) processes involving animals that cause suffering to them without any substantial medical benefit for humans or animals resulting from such processes.

[53] In claims with the wording "Processes for cloning mammal cells", it is understood that the word "mammal" includes human beings. Thus, such a claim might adversely affect public morality, order and health and would consequently contravene article 18 (I) of the Brazilian IP Statute. In this case, the exclusion of human mammals from the scope of the protection would be an acceptable disclaimer, even if human beings were not excluded in the original specification.

4.3.2 Non-patentable inventions as they fall under article 18 (iii) of the Brazilian IP Statute

[54] Pursuant to article 18 (III) of the Brazilian IP Statute, "living beings, in whole or in part, except transgenic micro-organisms meeting the three patentability requirements – novelty, inventive step and industrial application – provided for in article 8 and which are not mere discoveries" are not patentable.

[55] With regard to transgenic microorganisms, the sole § of article 18 (III) of the Brazilian IP Statute states that: "For the purposes of this statute, transgenic micro- organisms are organisms, except the whole or part of plants or animals, which exhibit, due to direct human intervention in their genetic composition, a characteristic that cannot normally be attained by the species under natural conditions".

[56] Pursuant to this definition, the expression transgenic microorganism encompasses microorganisms (see item 5) that are obtained through any technique whose outcome is an alteration in the genetic composition that is not attainable by the species under natural conditions, through direct human intervention. This definition is not limited to microorganisms in which genes have been inserted that are exogenous and/ or from other organisms.

[57] In order to examine claims for transgenic microorganisms, it is initially necessary to ascertain whether, in the description of the application, the term "microorganism" encompasses animal and plant cells which are not liable of patent protection, as the whole or part of plants and animals is not patentable, even if transgenic. In these cases, the claimed subject matter must be limited in a manner that encompasses only transgenic microorganisms liable of patent protection. Furthermore, the human intervention must be clear in order to assess whether it does, actually, refer to a microorganism that expresses a characteristic normally not attainable by the species under natural conditions.

[58] Denominations such as "transgenic", "mutant" or "variant" are not sufficient to ascertain the patentability of the microorganism, as there is a possibility of the microorganism, although referred to as "transgenic", "mutant" or "variant", to naturally occur or to be indistinguishable from its natural counterpart and, thus, not constitute an invention under article 10 (IX) of the Brazilian IP Statute.

5 Microorganisms

[59] The generic term “microorganism” is used for bacteria, archaea, fungus, single- cell algae not classified in the Plant Kingdom and protozoa. Thus, among the whole or part of living beings, whether natural or transgenic, the Brazilian IP Statute only allows the patenting of transgenic microorganisms.

Examples of appropriate formulations for microorganisms claims (non- exhaustive list)

- Transgenic microorganism characterized by containing SEQ ID NO: X.
- Transgenic microorganism characterized by containing SEQ ID NO: X inserted in the Y position of the genome.
- Transgenic microorganism characterized by containing the sequence xxxxxxx in the Y position of the genome (see item 2.2.2).
- Transgenic microorganism characterized by containing the gene X (provided the gene is well known).
- Transgenic microorganism characterized by containing the gene X with the promoter Z inserted in the position Y of the genome (provided that the gene and the promoter are well known).
- Transgenic microorganism characterized by containing the expression vector X (provided that this vector is well known).
- Transgenic microorganism characterized by being ATCC-XXXX (deposit number).

[60] Attention must be paid when SEQ ID NO: X, gene X or plasmid X were isolated from a natural microorganism and not modified. In this case, a claim with a generic title of “microorganism” or “bacteria”, among others, will also protect the original microorganism that naturally has the above-mentioned gene, and will be subject to objection under the provisions set forth in article 10 (IX) of the Brazilian IP Statute.

6 Biological sequences

[61] In general, for patent applications that describe an invention whose development depends on amino acid and/ or nucleotide sequences, the following aspects must be noted: (i) the need to include the sequence in the application for the purposes of sufficiency of disclosure (article 24 of the Brazilian IP Statute); (ii) natural occurrence (article 10 (IX) of the Brazilian IP Statute); (iii) clarity, accuracy and support (article 25 of the Brazilian IP Statute) in the manner in which such molecules/ sequences are claimed; (iv) novelty (article 11 of the Brazilian IP Statute); (v) inventive step (article 13 of the Brazilian IP Statute); and (vi) industrial application (article 15 of the Brazilian IP Statute).

[62] The sufficiency of disclosure for biological sequences is addressed specifically in item 2.2.2.

[63] The novelty requirement, when related to biological sequences, follows the same general principle (see Examination Guidelines for Patent Applications, Block II), meaning that for an amino acid or nucleotide sequence not meeting the novelty requirement in view of the state of the art, all the amino acids or nucleotides must be exactly the same and be in the same order and, additionally in some cases, have the same structural formula as the sequence known in the art.

[64] Other points that inadequacies are usually found are discussed in the following topics.

6.1 How to characterize

[65] Having complied with the rules established in item 2.2.2 as a way of ensuring the clarity and accuracy of the claimed subject matter, the claim chart must refer to the biological sequences in question through the corresponding SEQ ID NO: (see item 2.2.2).

[66] It is noteworthy that a DNA or RNA must be defined by its sequence of nucleotides, while a protein, by its sequence of amino acids, in order to clearly define the subject matter of protection.

[67] In some cases, other forms of characterization for biological sequences may be accepted:

a) when the sequences are shorter than four amino acids or ten nucleotides, pursuant to Rule PR #187/2017, they must be characterized by the specific sequence;

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

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

d) deposit number (see item 2.2.1); or

e) their name or designation, when the biological sequence is already known at the state of the art and is not the main purpose of the invention.

[68] In addition, degenerated sequences of a DNA or RNA defined by a nucleotide SEQ ID can be accepted, as long as they generate the same protein and that such protein is precisely defined (see acceptable types of writing below). In this situation, the SEQ ID of reference nucleotides must be disclosed in the application as filed.

[69] In general, the codons preferably used in most organisms of interest or model are already well established in the art (for example Escherichia coli, Saccharomyces cerevisiae, Arabidopsis thaliana, Zea mays, Glycine max, Drosophila melanogaster, Caenorhabditis elegans etc.). Thus, it is not considered undue experimentation to determine what the degenerate sequences would be when expressed in each of these organisms.

[70] On the other hand, in cases where the application involves the determination of the preferred codons in species that were little studied at the time of the invention, or the optimization of expression in specific organisms, the claim of degenerated sequences would not be acceptable. It is understood that in these situations the person skilled in the art would not be able to determine which sequences to use for the expression of the protein without incurring undue experimentation.

[71] It should be noted that biological sequences not disclosed in the application as filed may not be included later (even if such sequences can be deduced by a person skilled in the art), for incurring an addition of subject matter see article 32 of the Brazilian IP Statute. However, when the sequence of nucleotides or amino acids is known in the prior art and is still duly referenced in the specification, its subsequent presentation is acceptable (see also item 2.2.2).

Acceptable types of writing

- Nucleic acid molecule characterized by the nucleotide sequence of SEQ ID NO: X.
- Protein characterized by the amino acid sequence of SEQ ID NO: Y.
- Nucleic acid molecule characterized by the nucleotide sequence of SEQ ID NO: X, and degenerated sequences thereof, which code the amino acid sequence of SEQ ID NO: Y.

[72] In addition, attention must be paid to claims of the following types, since none of them are clear (article 25 of the Brazilian IP Statute).

a) DNA sequence characterized by encoding a protease.

In this type of claim, the product is characterized only by its function, that is not sufficient to clearly define which product it refers to. On the other hand, if this DNA is characterized by its nucleotide sequence, the definition of the function may be accepted, as an additional characteristic of the product.

b) DNA sequence characterized by coding a polypeptide presenting the amino acid sequence of the protein represented by SEQ ID NO: 1

This wording defines a DNA by the sequence of amino acids, which is not allowed. However, the claim could be altered in order to define the DNA by the nucleotide sequence, and its degenerations can be accepted, as defined in § [68].

c) Protein characterized by presenting the Y activity.

The product is characterized only by its function, which does not allow a clear definition of its scope. On the other hand, if the above-mentioned protein is characterized by its amino acid sequence, the definition of the function may be accepted, as an additional characteristic of the product.

d) Protein with the Y activity characterized by presenting the following amino acid composition: (percentage of each amino acid).

In this type of claim, the product is characterized by its function and percentage of amino acid, which also does not allow a clear definition of the claimed product. The amino acid sequence 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, which does not allow a definition of the product.

6.1.1 Markush sequences

[73] Biological sequences may be presented in the form of a Markush formula containing one or more variable sub-structures, which are accompanied by a list of definitions of these variable portions, such as:

Formula I peptide

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.

[74] Additionally, for Markush of nucleotides, a standard code for base alternatives can be used, which can be consulted in Table 1 of the Annex of the Rule which provides for the presentation of “Sequence Listing” in electronic media (currently Rule PR # 187/2017).

[75] For more details on Markush formulas, see the Examination Guidelines for Patent Applications, Block II.

[76] In the analysis of claims of this type, attention should be paid to the unit of invention criteria specific to the Markush groups, as Examination Guidelines for Patent Applications, Block I; as well as the possibility of occurring alternatives existing in nature (see item 4.2.1).

[77] Regarding the reasoning of alternatives in a claim containing a Markush formula of amino acid sequences, it is necessary to evaluate (i) the physical-chemical characteristics (polarity, size, charge, etc.) of the amino acids claimed for each position, in view of what was embodied in the specification; and (ii) the region in which the modifications occur, since in critical areas to the function of the polypeptide, even conservative modifications can generate very different results. In this sense, as non- exhaustive examples of acceptable amino acid substitutions we have: aspartic acid for glutamic acid; asparagine for glutamine; leucine to valine. As unacceptable examples (without due embodiment) we have: leucine for arginine; alanine for tryptophan; valine for proline.

[78] Regarding the Markush of nucleotide sequences, it is necessary to evaluate whether the sequence is a sequence coding for a protein or not. In the case of coding sequences, alternatives that generate the same protein are acceptable (see also § [68]). If the claimed sequence is not a coding one, the evaluation of the alternatives must take into account the information present in the Specification. For example, in the case of promoters, since the similarities/ differences in the physicochemical characteristics of the bases are not sufficient for a person skilled in the art to be able to predict which modifications would be equivalent, only the sequences embodied can be accepted.

6.1.2 When it is necessary to file the sequence listing with the application

[79] Rule PR # 187/2017 of the Brazilian PTO establishes in its article 2 that when the patent application contains one (or more) nucleotide and/ or amino acid sequence(s) that is/ are fundamental for the description of the invention, this/ these sequence(s) must be presented in a sequence listing.

[80] When the invention includes the sequence per se, that is, when the claim chart includes claims for "protein, "polypeptide", "nucleic acid", or any other term designating a biological sequence, it is considered a fundamental part of the invention, and must be included in the sequence listing (except for sequences of less than four amino acids or ten nucleotides, pursuant to the definition set forth in Rule PR # 187/2017).

[81] On the other hand, when the molecule in question is only an illustrative example, such specific sequence may not be considered as a fundamental part of the invention, and consequently, its sequence does not, necessarily, need to be presented as part of the application.

[82] Furthermore, attention must be given to the possibility that other sequences used in the application – but not necessarily the coding genes/ sequences – are fundamental for carrying out the invention. Thus, even in these cases, attention must be paid to whether the sequence in question is widely known at the art, and whether its use is fundamental for carrying out the invention.

6.1.3 Regarding the need to restrict process claims to the sequences filed with the application

[83] When the sequence in question merely represents a molecule that is part of a described process, but any other molecule with the same biological function would present the same outcome (or in situations where there is no reason to believe that such molecules will not be effective), such method does not necessarily need to refer to a single SEQ ID NO: X, as this would unnecessarily limit the scope of the method in question.

Example 16:

The application describes a method for inducing sporulation in bacteria characterized in that said bacteria are transformed by a vector containing the sporulation gene under the control of any promoter. The examples presented in the application use the spo5 gene, however, any gene in the spo family would, theoretically, allow the same outcome to be attained. Thus, in principle, there is no reason to present the specific sequence of the spo5 gene in the claim for such method.

Attention must be paid in these cases to the "generic" name given to the sequence of interest, such as "spo gene", as mentioned above, if the applicant uses such denomination in the claims, it must be widely known and used at the art, unmistakably referring to a specific gene family.

Example 17:

Method for inducing the expression of a specific gene under specific determined conditions.

The specification makes it clear that the desired characteristic is gene expression under a specific condition, which is attained only through the use of a promoter X, since such such promoter is only activated when the medium achieves certain characteristics of interest (glucose depletion, for example).

The application describes the use of different genes under the control of this promoter X, demonstrating that all of them are expressed only under the conditions of interest.

In this case, the only fundamental sequence for obtaining the desired characteristic is that of the promoter X. Consequently, similar to the previous example, the presentation of the sequences of the genes used is not mandatory; and even if the applicant has presented such sequences, it is not considered to be necessary that the claimed subject matter should be limited to these genes. However, the promoter sequence, which is the invention, must be described in a clear and precise manner by its corresponding SEQ ID NO.

6.2 Homology, identity and similarity

[84] When aligning and comparing nucleotide or protein sequences among themselves, the terms homology, identity and similarity may be employed. Initially, it is appropriate to point the correct distinction among these terms herein.

[85] Two sequences (of nucleotides or amino acids) are homologous only when they share a single common ancestor. In this sense, the concept of being "partially homologous" does not exist: two sequences are either

homologous or not, being incorrect to mention percentage of homology. Homologous proteins generally share many similarities in their three-dimensional structures. When two sequences are homologous, they generally share a significant identity, with the opposite also occurring: two molecules may be homologous without sharing any statistically significant identity between their amino acid or nucleotide sequences (for example, as is the case of the globins family).

[86] The establishment of homology between two sequences is not based only on the analysis of the identity between these sequences, but also on biological criteria, such as analyses of the structure and functions of the proteins, for example. Results of sequence comparisons through algorithms such as BLAST, FASTA and SSEARCH do not evaluate homology between sequences: they measure the similarity and identity among sequences. While homology refers to a qualitative inference, identity and similarity are quantitative attributes.

[87] The identity between two sequences refers to the occurrence of exactly the same nucleotides or the same amino acids in the same position in two nucleotide or protein sequences that are aligned and compared. In this sense, if two proteins present 90% identity, this means that 90% of all the amino acid residues in said proteins have identical corresponding positions.

[88] On the other hand, the percentage of similarity between two protein sequences refers to a calculation that takes into account identical and similar matches (for example, the glutamate and aspartate amino acids are considered similar, as both are acidic). It must be noted that similarity might be measured on the bases of different definitions of how closely related (similar) one amino acid residue is to another.

[89] 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 the SEQ ID NO: 1 or any other amino acid sequence with at least x% homology with SEQ ID NO: 1” is not clear (contravening the provisions of article 25 of the Brazilian IP Statute), as, technically, the term “% homology” is not applicable, as stressed above; and

b) claim of the type “DNA (or protein) sequence characterized by presenting at least 80% identity (or similarity) with SEQ ID NO: 1” cannot be accepted as the manner in which it is worded encompasses countless different sequences, not even specifying at what locations on the nucleotides (or amino acid) sequence such substitutions might occur; consequently, claims of this type may not be accepted, as the characterization of the subject matter of the protection is not clear and precise, contravening article 25 of the Brazilian IP Statute.

[90] Additionally, the characterization of the sequence of interest based on the identity percentage is very broad-ranging and generally includes in its scope sequences that are not supported by the specification or that fail to comply with the patentability requirements. Finally, it must also be noted that in these cases the specification generally does not provide sufficient information that would allow the replication of all the countless sequences encompassed by this type of definition (contravening article 24 of the Brazilian IP Statute).

6.3 Nucleotide sequences

[91] Nucleotide sequences may be mentioned in patent applications in different ways: genes, vectors, plasmids, DNA sequence, RNA sequence, nucleic acid, oligonucleotides, primers, cDNA, and others. However, for the purposes of simplification, in these Guidelines, all these molecules shall be generally called “nucleotide sequences”. This definition is valid, regardless of the size of the molecule in question. The following items discuss the particularities of some of these molecules.

[92] These nucleotide sequences must be characterized as set for in item 6.1. However, it must be stressed that molecules defined by a sequence of at least ten nucleotides must be characterized by its specific nucleotide sequence.

6.3.1 Modification of nucleotide sequence(s)

[93] Modifications of nucleotide sequences intended to distinguish them from natural sequences may be performed in different ways. In principle, any characteristic introduced in the sequence that is not described as naturally occurring is accepted as a modification, so as not falling under article 10 (IX) of the Brazilian IP Statute, and compliant with the provisions set forth in item 6.3.1.1. However, merely introducing terms such as "recombinant" in natural molecules' claims cannot be accepted, as the resulting molecule would be indistinguishable from its natural counterpart, even if produced in a recombinant manner.

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

[94] In general, modifications of natural biological sequences through the insertion of non-modified nucleotides in the sequence (in the middle or at the ends) are considered sufficient to avoid falling under article 10 (IX), provided that the resulting sequence formed does also not occur naturally.

[95] If the deleted nucleotides are in the middle of the claimed sequence, such modification is, in principle, sufficient to distinguish it from the natural molecule. However, even if the deleted nucleotides are contiguous and at the end of the sequence it still falls under article 10 (IX), as the resulting sequence would still continue to be identical to a part of the natural sequence (see item 6.3.2).

[96] With regard to the substitution of nucleotides by other non-modified nucleotides, it is considered that such modification is sufficient to avoid falling under article 10 (IX), provided that there is no description of natural sequences (for example, in related species) containing such substitution

[97] However, it must be borne in mind that many substitutions of nucleotides in a given sequence may not result in any modification in the protein encoded by this sequence, due to the degeneration of the genetic code. Consequently, in these cases, a nucleotide sequence modified by substitutions might not fall under article 10 (IX) of the Brazilian IP Statute, while the amino acid sequence encoded by this sequence remains identical to its natural counterpart, consequently falling under article 10 (IX).

[98] When analyzing sequences derived from the state of the art that do not fall under the provisions of article 10 (IX) of the Brazilian IP Statute, the inventive step of the modification carried out (insertion, deletion or substitution) must be assessed carefully, taking into account the fact that some groups of amino acids present common properties. Thus, the inventiveness of these alterations in the polynucleotide sequences, in general, depends on the demonstration of an unexpected effect generated by the modification compared to the state of the art.

6.3.1.1.1SNPS

[99] The SNP acronym refers to a "single nucleotide polymorphism", and is used to designate natural variations that occur in the genome and which involve, as the name indicates, a single nucleotide. They may be associated with certain characteristics, thus serving as molecular markers.

[100] Regardless of the described use, whenever a specific SNP – or any other polymorphism – is described as naturally occurring, it may not be considered as an invention under article 10 (IX) of the Brazilian IP Statute. However, the use of a set of SNPs, for example, in an in vitro diagnostic method (such as DNA fingerprinting) or in the personalized medicine field, might be liable of patent protection.

6.3.1.2 Modification of nucleotide sequence(s) with modified derivatives (including protecting groups)

[101] The insertions of nucleotides that do not occur naturally (derived from natural nucleotides) are also considered modifications sufficient for the sequences to avoid falling under article 10 (IX) of the Brazilian IP Statute. However, the presence of these nucleotides and the list of nucleotides of interest must be stated in the claims, in order to avoid the natural nucleotides of being indirectly included, resulting in the natural biological sequence.

[102] The inclusion of such nucleotides in the sequences presented in the patent applications is addressed in Rule PR # 187/2017 of the Brazilian PTO, as mentioned in item 2.2.2 of these Guidelines; and a list with examples of modified nucleotides and the acceptable acronyms for their definition is Available at Table 2 of the Annex appended to this Rule (published in the Federal Official Gazette (DOU) - Section 1, # 68, April 10, 2013).

6.3.2 Fragments

[103] Particular attention should be given to the analysis of claims involving "fragments of sequences", even though these sequences are included in the application. This remark is due to the fact that the definition of the "fragments" of a specific sequence includes all and any subdivision of the sequence presented, resulting in an undefined number of possible fragments that do not present any function/ relation to the subject matter described in the application.

Example 18:

An application presents a sequence SEQ ID NO: 1 (hypothetical): agctggttcgactgtctcga. The claim refers to the "nucleic acid characterized by having the nucleotide sequence SEQ ID NO: 1 and f ragments thereof". In the manner in which it is described, such claim includes, for example, molecules such as: agct, actg, ctgg, ggtt, ggttc, cgactgt, and countless others, including many that have no function described or related with the invention.

It is thus clear that the reference to the fragments of the specific sequence would not be acceptable in the claims, as the claimed subject matter lacks support and is not clearly and precisely defined as stipulated in article 25 of the Brazilian IP Statute. In these cases, the sufficiency of disclosure of the subject matter might be queried, pursuant to article 24 of the Brazilian IP Statute.

[104] On the other hand, if the application describes which fragments obtained from a given sequence are useful for the purpose described in the invention, such fragments can be claimed, provided that the desired fragments are clearly identified in the claims (specifying the position of the initial and final nucleotides of such fragment) and are not natural.

6.3.3 Oligonucleotides (or primers)

[105] As they represent segments of complementary sequences to genes and/ or natural mRNA, it is considered that primers form part of natural biological materials, and consequently claims addressing such primers falls under article 10 (IX) of the Brazilian IP Statute (note the possible exceptions in item 6.3.1).

6.3.3.1 Degenerated and modified oligonucleotides

[106] Degenerated oligonucleotides generally consist of a mixture of oligonucleotides that might be used to amplify genes with sequences that are similar, but not identical (such as the amplification of orthologous genes in related species), or even unknown genes.

[107] Attention must be given to the possibility that some of the resulting oligonucleotide(s) may be identical to a natural biological sequence (for example, to the sequence of the gene that it is intended to amplify), in this case falling under article 10 (IX) of the Brazilian IP Statute. On the other hand, should it present modifications that result in a nucleotide sequence that differs from those found in nature, it will not fall under the provisions of article 10 (IX) (see item 6.3.1).

[108] Moreover, taking into account that a mixture of oligonucleotides (for example, degenerated oligonucleotides, etc.) might not be clearly and precisely defined, claims related to such subject matter fail to comply with article 25 of the Brazilian IP Statute. Attention must also be paid to the description of this mixture in the specification (pursuant to article 24 of the Brazilian IP Statute).

[109] On the other hand, in order to define the claimed subject matter clearly and precisely, a degenerated

oligonucleotide might be characterized on the basis of a consensus sequence, varying in only one or a few pre-defined nucleotides. In these cases, claims for these degenerated oligonucleotides must mention the consensus sequence and the positions of the variable nucleotides.

6.3.4 Promoters

[110] The promoter is central to the process of the regulation of a gene, as it contains the binding sites for RNA polymerases responsible for genetic transcription. By definition, this constitutes the 5' regions of the gene. Processes resulting in transcriptional modulation are extremely complex and occur through 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).

[111] In contrast to gene sequences with specific markers at the starting and ending points (for example: initiation codon, polyadenylation site, etc.), a promoter sequence does not present such delimitations. Thus, experimental data must be presented proving that the isolated DNA sequence can result in the expression of gene sequences, meaning that it presents the promoter activity of interest.

[112] There are intermediate cases in which a DNA sequence with promoter potential is isolated, sequenced and analyzed through bioinformatics technology for predicting possible regulatory motifs (CCAAT box, TATA box, CpG islands, etc.). Although of great value for preliminary studies, such in silico analysis is not sufficient to demonstrate that the identified sequence is in fact a promoter region, and adequate functional assays are required for validation.

[113] Nevertheless, as they consist of nucleotide sequences, the promoters must be represented by a sequence SEQ ID NO: X, as established in items 2.2.2 and 6.1.2.

Example 19:

Claim: DNA sequence characterized by being the SEQ ID NO: 1

The above-mentioned sequence was isolated and presents promoter activity: such claim might not be accepted as it falls under article 10 (IX) of the Brazilian IP Statute.

However, in cases where the SEQ ID NO: 1 presents mutations, deletions and/ or insertions, meaning that it has become different from the sequence as it is found in nature, examination of novelty, inventive step and industrial application for the invention is required. It must be noted that deletions may result in fragments that are considered as part of the natural material, and would thus, fall under article 10 (IX) (see items 6.3.2 and 6.3.3.1).

Example 20:

Claim: Expression cassette characterized by comprising the promoter sequence SEQ ID NO: 1 operationally linked to a gene of interest and a terminator sequence.

Should the SEQ ID NO: 1 have been obtained from nature, and subsequently modified (through specific mutations, deletions and/ or insertions), the above claim might be accepted, provided that the subject matter is deemed to be novel and inventive. Should the SEQ ID NO: 1 be as found in nature, the claim must be restructured in a manner that better specifies the cassette, by introducing the term "heterologous", making it clear that it does not encompass protection for subject matter that falls under article 10 (IX) of the Brazilian IP Statute (see item 6.3.5).

Example 21:

Claim: Expression cassette characterized by comprising the promoter sequence selected from group of SEQ ID NO: 1 to 3 or fragments and derivatives thereof operationally linked to a heterologous gene of interest and a heterologous terminator sequence.

This type of claim must be analyzed by taking into account the remarks on the above examples. Furthermore, with regard to the promoter sequence, this must be limited only to the sequences for which the promoter activity of interest has been demonstrated. Should the promoter activity been demonstrated only for the SEQ

ID NO: 1, for example, the claim must be limited to said sequence; furthermore the expression “or fragments and derivatives thereof” might not be accepted, as the claimed subject matter is not properly supported or clearly and precisely defined in compliance with article 25 of the Brazilian IP Statute. In these cases the sufficiency of disclosure of the subject matter might be queried, pursuant to article 24 of the Brazilian IP Statute.

6.3.5 Vectors

[114] A vector is a DNA molecule used as a vehicle for the transfer of exogenous genetic material to other cells. Normally, the DNA vectors present three characteristics:

(i) they contain an origin of replication that allows their replication independent of the host chromosome; (ii) they contain a selection marker that allows the cells containing a vector to be easily identified; and (iii) they present single sites for one of more restriction enzymes. The cloning vector is intended to replicate an insert in a host cell. The expression vector contains an expression cassette that allows the insert to be expressed in the target cell in an induced or constitutive manner. The expression cassette contains regulatory sequences, such as promoter sequences and transcription terminator sequences.

[115] With regard to sufficiency of disclosure as set forth in article 24 of the Brazilian IP Statute, the examiner must analyze the invention in question and the level of details needed for its replication, depending, for example, on whether the vector is the main invention or an accessory invention. Along these lines, some aspects must be noted in the specification:

- the drawing representing the map of the vector in question, highlighting the characteristics that are essential for its functioning, meaning the cleavage sites for the restriction enzymes, the appropriate restriction enzymes, the promoter used, the repression regions, the termination regions, themarker 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 must be present in the sequence listing, as set forth in the Rule(s) in force;
- should the preferred codons for the expression of the insert in a specific microorganism be essential to the invention, they shall be included in the sequence listing; and
- the procedures and conditions for DNA/ RNA manipulation, including the enzymes used (for example, endonucleases, polymerases, ligases, etc.), the cloning systems involved, and the transfection/ transformation conditions of a host cell, among other usual techniques.

[116] It must be stressed that when there is no other way of defining the vector in a replicable manner (sufficiency of disclosure – article 24 of the Brazilian IP Statute), the biological material must be deposited (see item 2.2.1).

[117] Some examples of claims designed to reflect everyday situations in which the vectors are recombinants are presented below. In other words, these examples do not encompass natural vectors found in bacteria, fungus and plants, especially in mitochondria and chloroplasts, as these are not considered to constitute inventions as set forth in article 10, item IX, of the Brazilian IP Statute.

Example 22:

Vector as the main invention

Claim: Vector characterized by consisting of the filing number XXXX.

The main invention is a new and inventive vector that might be used for cloning and/ or for the expression of a gene of interest. In this case, the vector might be characterized in a claim by its deposit number issued by an International Deposit Authority. Thus, the vector will be clearly and precisely defined as set forth in article 25 of the Brazilian IP Statute.

Example 23:

Vector as the main invention

Claim: Vector containing the sequence of origin of replication, selection marker sequence and multiple cloning sites characterized by comprising the SEQ ID NO: X.

In this example, the vector structure is new and inventive due to the specific combination of the 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 restriction enzyme sites. Therefore, the essential elements that distinguish such vector from others constituting the state of the art must be the only elements characterized by their respective SEQ ID NO: X, as the other components are known to a person skilled in the art. It must be stressed that, in this case, the SEQ ID NO: X does not correspond to the expression cassette.

Example 24:

Vector as inter-related invention

Claim: Vector characterized by comprising of the sequences defined by SEQ ID NO: X and SEQ ID NO: Y operatively linked to the heterologous promoter and terminator sequences.

The invention describes two gene sequences involved in the transport of lysine that were isolated from Corynebacterium glutamicum. The SEQ ID NO: X encodes the lysine exporter protein (LysE), while sequence SEQ ID NO: Y encodes the regulatory protein (LysG) of LysE. Although the SEQ ID NO: X and SEQ ID NO: Y are endogenous of the Corynebacterium host cell and, consequently, natural, they are flanked by heterologous genetic construction sequences present in the recombinant vector. Consequently, the vector does not fall under the provisions set forth in article 10 (IX) of the Brazilian IP Statute.

Example 25:

Vector as inter-related invention

Claim: Vector characterized by comprising a DNA construct that consists of the sequence defined by the SEQ ID NO: X operationally linked to the promoter and terminator transcription sequences.

The invention refers to a new gene sequence that is endowed with inventive step and is liable of cloning/ expression in appropriate host cells.

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

6.3.6 CDNA

[118] cDNA molecules represent sequences produced from RNAs. In the case of cDNAs originating from messenger RNAs (mRNA), if the gene has introns, the cDNA will be different from the gene that encoded such mRNA, as the cDNA sequence will only have the sequence of exons. Thus, in these cases, it may not be considered that a cDNA molecule is the same as a natural molecule, and its patentability must be assessed on the basis of the requirements of novelty, inventive step and industrial application.

[119] When the cDNA refers to molecules produced from mRNAs of genes that do not have introns, such cDNA will have the same constitution as the strand of DNA/ gene that served as the template for the synthesis of such mRNA. Thus, in these cases, the cDNA is not considered to constitute an invention under article 10 (IX) of the Brazilian IP Statute.

[120] In the cases in which a cDNA is obtained from other types of RNA (such as tRNA, snRNA, rRNA), it should be verified if they are identical to the natural DNA, in which case they would not be considered inventions under article 10 (IX).

[121] Moreover, the simple sequencing of a cDNA without associating a function to it, is not sufficient to ensure its industrial application (see item 1.1) and the support for the subject matter, failing to comply with

articles 15 and 25 of the Brazilian IP Statute, respectively.

6.3.7 ESTs – expressed sequence tags

[122] The acronym EST refers to a partial sequence – or a fragment of a sequence – obtained from a cDNA (which is why it refers only to expressed sequences).

[123] The simple sequencing of an EST is not sufficient to ensure industrial application and support for the subject matter, failing to comply with articles 15 and 25 of the Brazilian IP Statute, respectively.

[124] In addition, in order to avoid falling under article 10 (IX), an analysis of such subject matter follows the same criteria used for cDNA; whereby it is necessary to know if the said EST represents a fragment of sequence from a single exon (in which case it would be considered as part of the natural biological material), or if it extends beyond the junction point between two different exons (in which case there is no natural equivalent, and it could, consequently, be considered to constitute an invention).

[125] On the other hand, when referring to sequences derived from genes that do not have introns, any EST is considered to be a fragment of a natural biological sequence (see also item 6.3.2).

6.3.8 ORFs – Open reading frames

[126] The acronym ORF refers to potential coding sequences generally obtained from DNA sequencing. Furthermore, an ORF has a start codon (related to a methionine, for most organisms) and ends with a stop codon.

[127] As it is a region of the genome, the ORF is deemed to constitute a natural product, thus not being considered to constitute an invention under article 10 (IX) of the Brazilian IP Statute.

[128] An ORF represents a candidate of a coding region of the genome, that does not necessarily result in a function or gene product. Thus, for a claim of the type “vector characterized by comprising the ORF present in SEQ ID NO: 1”, it is necessary to assess the demonstration of the functionality of the product obtained by the expression of such ORF in order to comply with the industrial application requirement (article 15), as well as the clarity and accuracy of the claimed subject matter (article 25 of the Brazilian IP Statute).

6.3.9 RNAs

[129] RNAs encoded by natural genes are also natural biological molecules and are, consequently, not considered to constitute inventions under article 10 (IX) of the Brazilian IP Statute.

[130] On the other hand, should they result from the expression of chimeric genes (such as genes constructed to express fusion proteins and/ or others not found in nature), these RNA molecules can not be considered as natural biological material.

6.4 Amino ACID sequences

[131] For the purposes of definition, when analyzing patent applications, it is considered that “proteins”, “peptides” and “polypeptides” must be defined on the basis of their linear amino acid sequence (primary structure), regardless of their size (total number of amino acid residues as set forth in Rule PR # 187/2017). Consequently, the mention to any of these terms (“proteins”, “peptides” or “polypeptides”) in these Guidelines shall, generally, refer to the “amino acid sequence” or the “protein sequence”.

6.4.1 How to characterize amino acid sequences

[132] As mentioned above, once the rules set forth in items 2.2.2 and 6.1 are complied with as a way of

ensuring the clarity and precision of the claimed subject matter, the claim chart shall refer to the proteins in question through the corresponding SEQ ID NO: and in some cases, additionally, by their structural formulas. In turn, sequences with up to 3 (three) amino acid residues must be represented throughout the entire application only by its sequence.

Example 26:

Acceptable claims for amino acid sequences (provided that these sequences do not occur naturally)

Claim: Protein X is characterized by comprising the amino acid sequence as defined in SEQ ID NO: 1.

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

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

Example 27:

Claims not acceptable for amino acid sequences.

Claim: Protein characterized by consisting of the amino acid sequence coded by sequence SEQ ID NO: 2 (nucleotide sequence).

In order to meet the requirements of art.25 of the Brazilian IP Statute, a protein must be defined by its corresponding amino acid sequence (see § [66]). The claim could be changed to define the protein by the amino acid sequence, provided it was disclosed in the application as filed (see § [71]).

[133] In this sense, the characterization of protein sequences will not be accepted only through their properties, such as three-dimensional structure, biological function or activity, name, chemical properties (PI, molecular weight, amino acid composition, etc.), since the only way to inequivocably clear and precise a sequence of amino acids is through its sequence.

[134] In addition, attention should be paid to item 6.2 of these Guidelines, which deals with the claim of biological sequences through percentages of identity and/ or similarity to a reference sequence.

[135] It should also be borne in mind that the use of the terms consists of or comprises results in differences in the scope of the claim (see the Examination Guidelines for Patent Applications, Block I).

Example 28:

The specification of the application describes a mutated (not natural) protein that is characterized by consisting of the SEQ ID NO: W. In this case, it would not be possible to accept a generic claim claiming protection for a mutated (not natural) protein that is characterized by c omprising the SEQ ID NO: W, as this would introduce the possibility of any extension in the carboxy and/ or amino terminal regions of the protein that could result in alterations to its three-dimensional structure and/ or alterations in function. Consequently, it would not be possible to state that any protein that comprises the SEQ ID NO: W would have a similar function to the protein that consists of the SEQ ID NO: W, with such claim being rejected due to the absence of sufficiency of disclosure and support in the specification (articles 24 and 25 of the Brazilian IP Statute). Even if the specification discloses some possible extensions in the amino acid sequence of the protein, such examples would not be sufficient to support that any extension would achieve the same results.

6.4.2 Homologous proteins (paralogous and orthologous)

[136] Homologous proteins are proteins derived from an “evolutionary common ancestor”. They may be present in a single species, deriving from gene duplication, originating what is called paralogous (equivalent proteins – with or without sequence alterations produced in the course of evolution – found in the same species). On the other hand, they may be found in different species that have a common ancestor, in this case, these proteins are called orthologous.

[137] These definitions are important for assessing the inventive step of applications that describe and claim proteins similar to proteins whose functions are already known, differing only in terms of the organisms from which the protein is derived.

Example 29:

A patent application describes protein B, isolated from a specific species. Such protein B presents a sequence and activity which is very similar to another protein denominated A, previously described in the state of the art for a different species (A and B are, consequently, orthologous proteins). In these cases, the mere fact that protein B was isolated from a different organism does not necessarily make it inventive, compared to protein A. Thus, when assessing inventive step, it must be evaluated if protein B presents some unexpected characteristic compared to its orthologue A. Even so, in this case, protein B would not be considered as constituting an invention under article 10 (IX) of the Brazilian IP Statute.

[138] Moreover, when applications involve "variants" or "modifications" of natural proteins, attention must be paid to the scope of article 10 (IX) of the Brazilian IP Statute, as such modifications may result in another biological molecule that is proven to be natural, deriving merely from a species other than the one described in the application.

Example 30:

An application describes modifications in a bovine protein that make it appropriate for a specific use, and claims the modified protein. However, the protein resulting from the alterations introduced, such as substitutions, results in a sequence that is the same as the canine version of such protein, which is already known. In this case, even if it is not the same as the natural equivalent of the organism from which it was obtained, the claimed protein is the same as an orthologous protein – natural from another species –, and consequently, it also falls under the provisions of article 10 (IX) of the Brazilian IP Statute.

6.4.3 Protein fragments

[139] Similar to a protein, a protein fragment must be characterized by at least its amino acid sequence (see item 6.4.1). In this sense, when a protein fragment is claimed and characterized only by its linear sequence, the examiner must carry out a search for the characterizing amino acid sequence. Should the sequence be found in the state of the art as part of a protein or peptide that is of natural origin, the claimed subject matter will fall under article 10 (IX) of the Brazilian IP Statute, as it forms part of natural living being and/ or biological materials found in nature.

[140] When a peptide containing a small number of amino acids is claimed, it is likely that it will be found in some protein in nature, even with no known function in the protein or even in a context other than that of the subject matter presented in the application under examination. Nevertheless, the claimed subject matter falls under the provisions set forth in article 10 (IX) of the Brazilian IP Statute, as this PTO does not stipulate any demarcation for the minimum size of a fragment to constitute part of a natural biological material. Thus, any part of natural living beings and biological materials (i.e. fragments) found in nature may not be considered as constituting inventions.

[141] It is possible that a claimed fragment is identical to a part of an entire molecule found in nature. In these cases, even when the claimed fragment presents innovative activity, function, or chemical properties in view of the state of the art, as it constitutes part of a natural living being or a biological material found in nature, it does not constitute an invention under article 10 (IX) of the Brazilian IP Statute, thus there is no room for any type of analysis of its novelty and inventive step.

[142] It is important to note that the presence or inclusion of the term "recombinant" in a claim for natural molecules might not be accepted, as the resulting molecule would be indistinguishable from its natural counterpart, even if produced in a recombinant manner.

[143] In this sense, it is clear that any portion of a protein found in nature, regardless of the number of amino acids, must be considered as part of natural living beings and biological materials found in nature and will consequently not be deemed to constitute an invention under article 10 (IX) of the Brazilian IP Statute.

Example 31:

Claim: Peptide characterized by the sequence Ile-Leu-Arg.

Protection is claimed for a biologically active peptide obtained synthetically and with immuno-regulatory properties, consisting of three amino acids. After the search, it was shown that the sequence is contained in several natural proteins. The application argues that the peptide may be distinguished from the natural polypeptide in several aspects such as folding, spatial conformation, aggregation and physico-chemical properties.

Although differences may exist in the physical and chemical properties of the claimed molecule, compared to natural polypeptides that comprise the same sequence, the claimed peptide presents a sequence of amino acids found in nature, which is why the subject matter is not considered to constitute an invention under article 10 (IX) of the Brazilian IP Statute.

Example 32:

Claim: Protein characterized by having the SEQ ID NO: 1 in which positions 1 to 6 were deleted.

A cytokine having 76 amino acids when truncated at the sixth amino-terminal amino acid, began to exhibit an antagonist activity of the entire cytokine, and thus might be used for the manufacture of medicaments for treating diseases that require a cytokine antagonist.

Although human interference produced results in an innovative activity, such fact occurred merely by the deletion of part of the molecule, with the obtained sequence remaining identical to the 6-76 amino acid sequence found in the entire natural molecule 1-76. According to article 10 (IX) of the Brazilian IP Statute, such analogue is not considered as constituting an invention as it consists of part of a natural molecule, and thus, it is not patentable.

6.4.4 Modifications to the sequence

[144] Modifications of protein sequences intended to distinguish them from natural sequences can be made in different ways. In principle, any characteristic introduced in a sequence that has not been described as a natural occurrence is acceptable as a modification, whereby it does not fall under article 10 (IX) of the Brazilian IP Statute.

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

[145] As pointed out above for modifications in general, modifications in biological sequences through the insertion of natural L-amino acids in the sequence (in the middle or at the ends of the sequence) are considered as sufficient to avoid falling under article 10 (IX) of the Brazilian IP Statute, provided that the resulting sequence formed is also not found in nature.

[146] For the deletion of amino acids, the position of the deleted amino acid results in different situations to be taken into account. If located in a central part of the protein sequence, such modification is, in principle, sufficient to distinguish it from the natural molecule. However, if the deleted amino acids are contiguous and are located at the end of the sequence, it still falls under article 10 (IX) of the Brazilian IP Statute, as the resulting contiguous sequence is identical to part of the natural sequence (see Example 32).

[147] With regard to the substitution of amino acids by other natural amino acids, such modification is deemed sufficient for the sequence to avoid falling under article 10 (IX), provided that there is no description of any natural proteins in related species containing such substitution (see item 6.4.2 on orthologue proteins).

[148] When analyzing proteins already described in the state of the art, a careful assessment of the inventive step of the modification is required (insertion, deletion or substitution), taking into account 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, compared to the state of the art.

6.4.4.2 With non-natural amino acids (including protecting groups)

[149] Insertions of amino acids that do not occur naturally (derived from natural amino acids) are also considered to constitute modifications that are sufficient for the protein sequences to avoid falling under article 10 (IX) of the Brazilian IP Statute. However, for the purposes of clarity and precision, these amino acids must be appropriately identified in the claims, in order to avoid natural amino acids to be indirectly included, and thus, resulting in the natural biological sequence.

[150] The inclusion of such amino acids in the sequences presented in the patent applications is also addressed in Rule PR # 187/2017 of the Brazilian PTO, cited in item 2.2.2 of these Guidelines; and a list with examples of non-natural amino acids and the acronyms acceptable in their definition is Available at Table 4 of the Annex to this Rule.

6.4.4.3 Groups added to the carboxy or amino terminal

[151] A protein sequence might also be modified by binding chemical groups to its ends, in order to allow it to be anchored to a specific surface or structure, increase protein activity, modulate bio-availability and/ or circulating half-life, etc.

[152] Once again, attention must be paid to the manner in which such molecule is claimed, in order to ensure the presence of the chemical group in the molecule, as it is such group that will distinguish it from its natural equivalent. Fmoc, t-boc, other chemical groups, prosthetic groups, lipids, carbohydrates, iron, calcium and heme are examples of groups that, when added to proteins, may possibly distinguish them from their natural counterparts.

6.4.5 Fusion proteins

[153] By definition, these are proteins created by the union (fusion) of parts of two or more different protein sequences. In this sense, a fusion protein addressed by a patent application is formed by at least a "functional" portion responsible for the property related to the invention.

[154] Consequently, for the purposes of definition and in compliance with article 25 of the Brazilian IP Statute, it is important to stress that, for a fusion protein, all the functional portions in the final protein must be described in the application.

6.4.5.1 Of natural occurrence

[155] Rare cases of naturally expressed fusion proteins are noted in some types of cancer, due to chromosome translocation, which may result in the fusion of different genes, such as gag-onc, Bcr-abl, and Tpr- met fusion proteins.

[156] Once the occurrence of a natural identical structure has been proven, pursuant to the provisions set forth in item 4.2.1 (for example, Bcr- abl, with a portion 1-50 of Bcr fused to the abl 13- 78 portion), these proteins may not be considered to constitute invention under article 10 (IX) of the Brazilian IP Statute.

6.4.5.2 How to characterize it

[157] In general, when defining fusion proteins, the rules established for any other protein sequences are valid (see item 6.4.1). Thus, references to homology, similarity or identity percentages are not accepted, and the proteins shall be referred by at least one of their amino acid sequences or by the SEQ ID NO: corresponding to the functional portion.

6.4.5.3 Entire seq ID

[158] When the polypeptide sequence described in the patent application is claimed in the form of a fusion protein, it must always be characterized by at least its amino acid sequence or the corresponding SEQ ID NO:,

in order to define in a clear and precise manner the claimed subject matter related to the invention.

[159] When several peptides are related to the property described in the invention, and they are all present in the claimed fusion protein, all these peptides must be characterized by at least their amino acid sequence or the corresponding SEQ ID NO:.

[160] Special attention must be paid to cases in which the "fusion" protein is in fact formed by fragments of a same protein occurring naturally: depending on the manner in which it is claimed, the final protein produced (fusion protein) may turn out to be the same as the natural molecule.

Example 33:

Claim: Fusion protein characterized by the fact that it comprises:

a) a first polypeptide consisting of the amino acid sequence 41-56 of SEQ ID NO: 2;

b) a first spacer of 6-27 amino acids;

c) a second polypeptide consisting of the amino acid sequence 69-84 of SEQ ID NO: 2;

d) a second spacer of 5-11 amino acids; and

e) a third polypeptide consisting of the amino acid sequence 92-105 of SEQ ID NO: 2.

In this claim, as the spacers of interest are not defined, mentioning ranges compatible with the interval between the defined sequences, the scope of the resulting "fusion" protein encompasses in its scope the protein itself, the sequence of which is described in SEQ ID NO: 2, which occurs naturally, falling under article 10 (IX) of the Brazilian IP Statute.

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

[161] When the protein of interest is fused with another polypeptide that will serve merely as a "tag/ reporter", said reporter may be defined by its amino acid sequence or the corresponding SEQ ID NO:, as established previously for any polypeptides. However, if such "reporter" polypeptide is widely known in the state of the art, reference to it might, optionally, be made through its acronym, for example, the molecules such as GFP (green fluorescent protein), GST (glutatione S-transferase), CAT, c-Myc, FLAG, among others.

[162] An application may, eventually, present the type of situation in which the inventive characteristic of the fusion protein is found only in the presence of the protein described in the application – which might even be the reporter portion – and it may be fused to several others.

Example 34:

The application describes a polypeptide X that by itself does not have any surprising activity, but that can enhance the immunological response to antigens that are fused to it. In the claim chart a "fusion protein characterized by consisting of protein X (defined by its SEQ ID NO:) bound to an antigen" is claimed.

In this case, attention must be paid to the clarity and precision of the manner in which the fusion protein is claimed, as the antigen that is fused to it is not defined in the claim, and the decision to be taken must consider the information available in the specification.

Situation 1: The specification presents examples of protein X fused with several different unrelated antigens and demonstrates the undeniable efficacy of all the resulting proteins for the proposed purpose, with no indication that another antigen would not function in the same manner. In this case, it is not necessary to require the application to list all the possible antigens that could be used in the fusion protein, and it is considered that the claim is acceptable in the manner in which it is worded above.

Situation 2: The application presents examples of protein X fused with various different antigens, unrelated, but the results demonstrated are not consistent, showing that the fusion protein is effective for some antigens and not for others. In this case, the application does not provide sufficiency of disclosure and support in compliance with articles 24 and 25 of the Brazilian IP Statute to ground that the fusion protein functions with any antigen (it may include antigens for which there is no evidence that they function as described),

Consequently, the claim chart must be limited to the subject matter described and for which support is presented in the application in accordance with articles 24 and 25 of the Brazilian IP Statute, i.e., the claims must specify which are the antigens of interest present in the claimed fusion protein.

6.4.6 Antibodies

[163] Antibodies are plasma proteins that specifically bind to substances known as antigens, and include polyclonal and monoclonal ones; therefore, they must be analyzed as proteins, including the provisions of article 10 (IX) of the Brazilian IP Statute (see item 6.4 and its subitems).

[164] If the search determines that the antibody sequence already exists in nature, the antibody will be considered natural and, thus, will fall under article 10 (IX) of the Brazilian IP Statute (see also item 4.2.1). In addition, if the application clearly describes that the antibody was obtained from an organism naturally exposed to the antigen, the antibody is also considered natural, falling under article 10 (IX) of the Brazilian IP Statute.

[165] However, in many cases the antibody would not exist without significant human intervention, as it would depend on exposure to the antigen in a controlled and repeated manner, including the use of adjuvants, to ensure the activation of specific cells for the humoral response. In this sense, such an antibody and the process of obtaining it are not considered natural, given the understanding that human intervention is decisive for the final result. It should be noted that the way to define the antibody must be through its SEQ ID or the deposit of biological material.

[166] Polyclonal antibodies are derived from different B cell lines. They are a mixture of immunoglobulin molecules secreted against a specific antigen, each recognizing a different epitope. Thus, since they comprise an indeterminate mixture of antibodies, they are considered to have a problem of clarity and precision in defining their characteristics (article 25 of the Brazilian IP Statute). In addition, even though the process of obtaining these antibodies is described in detail, a person skilled in the art who performs such a method would not achieve the same final product, which results in a lack of reproducibility/ sufficiency of disclosure of polyclonal antibodies (article 24 of the Brazilian IP Statute).

[167] On the other hand, with respect to the claims for the process of obtaining polyclonal antibodies, it is possible for a person skilled in the art to reproduce the invention, as long as the steps of said method are sufficiently described in the application (article 24 of the Brazilian IP Statute). Additionally, it should be noted that the definition of the steps is also important so that the subject matter does not fall under article 10 (IX) of the Brazilian IP Statute (see item 4.2.1.2). Attention should also be given to the possibility of falling under article 10 (VIII) of the Brazilian IP Statute (for example, method for immunization/ vaccination).

[168] Monoclonal antibodies are antibodies specific for a single epitope of an antigen. Through human intervention, a monoclonal antibody can be obtained using different techniques, such as hybridoma (see item 6.4.6.1) or genetic engineering techniques. These techniques include the selection of individualized B cells (for example, by means of flow cytometry – FACS) with subsequent cloning of the immunoglobulin light and heavy chains.

Example 35:

Wording of claim for antibody liable of patent protection.

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

Claim: Antibody characterized by comprising the complementarity determining regions (CDR1; CDR2; CDR3) consisting 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 constant regions of human γ chain.

In the examination of this type of claim, the issues related to article 10 (IX) of the Brazilian IP Statute mentioned above (see § [164]).

Example 36:

Antibody claims that are not acceptable.

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

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

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

d) Claim: Monoclonal antibody characterized by comprising the complementarity determining region (CDR3) consisting of SEQ ID NO: X in the light chain and SEQ ID NO: A in the heavy chain and constant regions of the human □□chain.

As they do not clearly and precisely define the antibodies and/ or fragments that are being claimed, these claims cannot be accepted for being in disagreement with article 25 of the Brazilian IP Statute. In the case of the wording of item d) above, it is necessary to define at least the sequences of the 3 (three) CDRs of the chains present, in order to clearly and precisely define said antibody.

6.4.6.1 Hybridomas

[169] Hybridomas are the result of a fusion of two cell types, a myeloma and a lymphocyte B, and produce antibodies. They present characteristics that cannot be attained by these cell types under normal conditions, being the outcome of direct human intervention. As addressed in the understanding adopted by this PTO, from the technical point of view, a hybridoma is considered a transgenic microorganism, and such subject matter is thus patentable, as it does not fall under articles 10 and 18 of the Brazilian IP Statute.

[170] At the same time, as it refers to biological material that is essential for the practical embodiment of the subject matter of the patent application, and it cannot be characterized in a clear and precise manner in the specification, in order to comply with the sole § of article 24 of the Brazilian IP Statute, the filling of the hybridoma is essential by the filing date of the patent application or its priority date, with the presentation of the deposit number in the patent application (see item 2.2.1).

6.4.6.2 Antibodies obtained by genetic engineering

[171] Monoclonal antibodies of mice, rabbits, etc., when used as therapeutic agents in humans, can be recognized as foreign proteins by the human host's immune system. Thus, the advent of chimeric, humanized and "fully human" antibodies are mechanisms used to minimize such therapeutic obstacle.

[172] Chimeric antibodies are comprised of human Fc and non-human Fab regions. Humanized antibodies, in turn, have only the variable region of the non-human Fab fragment. In both antibodies, the sequences of the Fc and Fab regions are cloned into an expression vector for further cultivation of the transfected host cell and subsequent purification steps.

[173] Monoclonal antibodies called "fully human" are antibodies obtained by recombining human immunoglobulin genes. Such antibodies are currently obtained by two categories of techniques: libraries of recombinant antibodies assembled in vitro and transgenic mice.

[174] In the method of recombinant libraries, human genes for immunoglobulins are recombined in vitro and expressed in phages (phage display technique), yeasts, among others, in order to express the variable region of the antibody on its surface. From these libraries, the phenotype expressed on the surface can be used to select the recombinant clone that has the genotype of interest.

[175] In the method using transgenic mice, mice comprising sequences of human germline immunoglobulin genes are immunized for antibody production, and monoclonal antibodies are obtained by conventional methods (hybridoma or FACS isolation, followed by sequencing and recombinant expression).

[176] Although monoclonal antibodies called “fully human” (see § [173]) can potentially be generated in nature, their production depends on human exposure to the antigen in a controlled and repeated way, including the use of adjuvants, to ensure the activation of specific cells for the humoral response against the antigen. Thus, as discussed in item 6.4.6 above, such antibodies will not be considered natural, unless their sequence has already been proven to exist in nature (see item 4.2.1).

[177] In addition to chimeric/ humanized/ “fully human” antibodies, other technologies have been used. These include bi-specific antibodies, single chain antibodies, PEGylated antibodies, antibodies with altered glycosylation patterns or Fc portion, antibodies derived from camelids (nanobodies), antibodies fused with drugs or other proteins, among others. Such subject matter may be subject to protection as long as they are in accordance with patentability requirements.

Example 37:

Wording of antibody claims liable of patent protection.

Claim: Humanized antibody against α-actin characterized by comprising the variable murine region consisting of SEQ ID NO: X and regions constants in the human □□ chain. Claim: Humanized antibody against α-actin characterized by comprising the complementarity-determining murine regions (CDR1; CDR2; CDR3) that 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 constant regions of the human □ chain.

6.4.6.3 Antibody fragments

[178] The antibody molecule might be cleaved generating different fragments with distinct functions. Should the fragments originate from antibodies found in nature, or form part of other natural proteins, they are not liable of patent protection in view of article 10 (IX) of the Brazilian IP Statute (see item 6.4.3).

[179] It is noteworthy that fragments derived from antibodies not found in nature can still be considered natural if they contain only the constant portions (Fc) of the original antibody. Ultimately, such fragments are identical to the constant portions of other natural antibodies.

[180] Modifications to antibody fragments may also be liable of patent protection, as is the case of single chain variable fragments (ScFv). The Fv fragments are not covalently bound, therefore the VH and VL domain heterodimers can be easily dissociated. However, Fv fragments may be constructed in a manner whereby they do not dissociate, that is, the VH and VL domains may be linked by a connector, creating a single chain Fv fragment. Despite being an antibody fragment, such construction does not fall under article 10 (IX) of the Brazilian IP Statute, as these fragments are not found in nature linked by the connector.

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

7.1 Animals, plants and their parts

[181] If they are natural or isolated, they are not considered an invention, according to article 10 (IX) of the Brazilian IP Statute. When resulting from human genetic manipulation, they are not patentable, according to article 18 (III) of the Brazilian IP Statute.

7.1.1 Stem cells

[182] Stem cells are cells capable of differentiating into the tissues that make up the human or animal body, and can be obtained directly (i) from the embryo; (ii) from various tissues of the adult organism (such as bone marrow, adipose tissue); (iii) from umbilical cord and placental blood; or they can be obtained indirectly from the reprogramming of a differentiated adult cell (induced pluripotent stem cell – iPS).

[183] Embryonic stem cells can be obtained from the internal mass of blastocysts from embryos produced

by in vitro fertilization.

[184] Human embryonic stem cells are mentioned in article 5 of the Biosafety Law No. 11,105/2005, which provides:

"Article 5 For the purposes of research and therapy, the use of embryonic stem cells obtained from human embryos produced by in vitro fertilization and not used in the respective procedure is allowed, provided the following conditions are met:

I - they are non-viable embryos; or

II - they are embryos frozen for 3 (three) years or more, on the date of publication of this Law, or were, already frozen on the date of publication of this Law, after completing 3 (three) years, counted from the date of freezing.

§ 1 In any case, the consent of the parents is required.

§ 2 Research institutions and health services that carry out research or therapy with human embryonic stem cells must submit their projects to the appreciation and approval of the respective research ethics committees.

§ 3 The sale of biological material to which this article refers is prohibited and its practice implies the crime typified in article 15 of Law No. 9,434, of February 4, 1997."

[185] In response to the consultation carried out by CGPAT II on the application of the Biosafety Law to patent applications addressing processes or compositions involving human embryonic stem cells, the Specialized Federal Attorney's Office together with the Brazilian PTO expressed itself, by means of Opinion No. 00037/2018/PROCGAB/PFE- INPI/PGF/AGU, pointing out that it does not identify a legal obstacle to patenting products, processes for obtaining and applying human embryonic stem cells. The Attorney General clarified that the conditions set forth in article 5th for research and therapy purposes do not exist in equal measure for patenting; and that the commercial prohibition contained in article 5, § 3, of the Biosafety Law does not extend to patenting, since marketing and patenting are different activities.

7.1.2 Products and processes involving stem cells

[186] According to the Brazilian IP Statute, stem cells per se, obtained from an animal or with some genetic modification, are not liable to protection under the provisions of articles 10 (IX) or 18 (III), respectively. In cases where compositions or kits contain stem cells, such products can be considered patentable.

[187] The processes of obtaining/ cultivating stem cells and applying (uses) thereof can be considered patentable as long as they do not imply or include a therapeutic and/ or surgical method (article 10 (VIII) of the Brazilian IP Statute).

[188] The following are examples of subject matter that may be liable of patent protection:

- compositions containing stem cells and other ingredients (various implants containing cells, cell and matrix formulations, cells and growth factors, etc.);
- composition containing mixtures of different types of stem cells;
- processes of purification, preparation, conditioning, differentiation, reprogramming, or any processing of stem cells as long as it is carried out in vitro;
- uses of stem cells for the preparation of medicament to treat disease X;
- uses of stem cells for the preparation of implants to treat disease X;
- uses of stem cells for the preparation of compositions for the diagnosis of disease X;
- diagnostic processes that include steps that use stem cells or synthetic tissues, as long as they are performed in vitro;
- drug tests that include steps that use stem cells or synthetic tissues, provided they are performed in vitro;

- stem cell cultivation processes;
- conditioned culture media obtained during the cultivation of stem cells.

7.2 Transgenic plants, their parts and processes of obtaining them

[189] These are plants whose genomes have been modified by the introduction of a DNA manipulated by recombinant DNA techniques, and whose modification would not occur under natural crossing or recombination conditions.

[190] Transgenic plants and their parts (for example, transgenic cell, transgenic tissue and transgenic organ) are not considered as constituting patentable subject matter in accordance with article 18 (III and Sole §) of the Brazilian IP Statute.

[191] Even if the process of obtaining transgenic plants is patentable, it is important to stress that the intermediate and/ or final product resulting from such process, that is, the transgenic plant and/ or the parts of said plant constitute subject matter whose patentability is expressly forbidden in accordance with article 18 (III and Sole §) of the Brazilian IP Statute. However, there are no constraints on patenting the processes used for obtaining these plants, except for those involving use restriction technologies, see item 7.4.

Examples of claims liable of patent protection

- Production method of a transgenic plant characterized by the fact that it comprises the steps of:

(a) obtaining a plant explant;

(b) exposure of the explant to the culture of Agrobacterium tumefaciens containing the vector defined by claim X (properly described with a selection gene, a heterologous gene and the promoter sequence(s));

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

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

- Method for producing a transgenic dicot plant, characterized by the fact that it comprises:

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

(b) obtain a transformed plant cell; and

(c) regenerate from the transformed plant cell a genetically transformed plant.

7.3 Process of obtaining plants by crossing

[192] Article 10 (IX) of the Brazilian IP Statute establishes that natural biological processes are not considered to constitute inventions, and consequently excludes the patenting of natural biological processes, including those used to produce plants.

[193] "Natural biological processes" is understood as all processes that do not use technical procedures to obtain biological products or that, even if using a technical procedure, could occur in nature without human intervention, consisting entirely of natural phenomena. In this sense, biological processes shall be considered as not natural when direct human intervention is required in the gene composition, and the effect is permanent.

[194] Thus, processes involving the crossing of genetically modified plants through direct human intervention are liable of patent protection.

Example 38:

Non-transgenic parents.

Claim: Method for producing a plant X characterized by comprising the steps of:

a) selecting a homozygous plant X for gene A;

b) selecting a homozygous plant X for B gene; and

c) cross the plants selected in steps (a) and (b) to produce a hybrid plant.

Conventional methods of plant production based on steps of selection, crossing and propagation are considered natural biological processes, falling under the provisions of article 10 (IX) of the Brazilian IP Statute. In these cases, human interference through the selection and induction of specific crossings is not essential for the process to occur, only accelerating or limiting what would occur in nature.

(IX) of the Brazilian IP Statute. In such cases, human interference is not decisive for obtaining the final result, merely accelerating or limiting what would

Example 39:

Non-transgenic parents.

Claim: Method for producing a plant X with high levels of W compounds characterized by comprising the steps of:

a) identifying gene markers linked to high levels of W;

b) selecting individuals comprising the markers identified in step (a); and

c) crossing the individuals selected in step (b).

Conventional methods of plant production based on steps of selection, crossing and propagation in which human intervention consists only of providing additional technical means to facilitate or direct the process – In this case, the identification of genetic markers – are considered natural biological processes, falling under the provisions of article 10 naturally occur.

Example 40:

Transgenic parents.

Claim 1: Method for producing hybrid seed characterized by comprising crossing a herbicide-resistant plant with a plant with increased 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 with increased nutritional value characterized by comprising the steps of:

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

b) develop base populations;

c) individually evaluating the plants obtained; and

d) selecting plants with increased nutritional value including the herbicide resistance characteristic.

This process involves an essential technical step for obtaining plants that do not occur in nature and, therefore, does not fall under the provisions of article 10 (IX) of the Brazilian IP Statute.

7.4 Genetic technologies having use restriction

[195] According to the sole paragraph of article 6 of Law No. 11.105/05 (Biosafety Law), “genetic technologies having restriction of use are understood as any human intervention process for the generation or multiplication of genetically modified plants to produce sterile reproductive structures, as well as any form of genetic manipulation aimed at activating or deactivating genes related to plant fertility by external chemical inducers”.

[196] In this context, item VII of article 6 of the Biosafety Law prohibits "the use, commercialization, registration, patenting and licensing of genetic technologies having use restriction". In this sense, it is not allowed to patent human intervention processes for the generation/ multiplication of genetically modified plants with regard to the production of sterile reproductive structures.

[197] In response to the consultation carried out by CGPAT II on the applicability of the prohibition established in article 6 (VII) of the Biosafety Law, when examining patent applications that involve technologies having use restriction, the Specialized Federal Attorney's Office together with the Brazilian PTO manifested itself, through note 0182- 2012- AGU/PGF/PFE/INPI/COOPI-ALB-2.2, indicating that patent applications that fall under that prohibition shall be rejected. Such understanding was standardized in the BRPTO's Official Gazette # 2172 of August 21, 2012.

[198] Thus, when identifying in a patent application that the claimed subject matter falls under the scope of Law # 11,105/05, that is, in processes that involve technology having use restriction, the examiner must issue an objection based on article 6 (VII) of the Biosafety Law. In the subsequent examination, if the applicant maintains the process involving the technology having use restriction, the examiner may reject the application, on the same legal basis.

[199] For the purposes of these Guidelines, it is understood that processes and/ or genetic manipulation that produce sterile reproductive structures (pollen, egg, stigma, anther, fruit, and tissues thereof), or that aim at the activation or deactivation of genes related to the fertility of plants by external chemical inducers, fall under the prohibitions of article 6 (VII) of the Biosafety Law.

Examples of claims for processes involving unauthorized technology having use restriction:

- Method for producing a variety capable of having seedless fruits, characterized by the fact that a variety of male sterility having a parthenocarpic characteristic is backcrossed with a plant of a fixed lineage.
- Method for producing of a hybrid plant characterized by fusing protoplasts of a sterile male plant with protoplasts of a second variety, to confer the sterility characteristic to the second variety.

Examples of subject matters that do not fall under the prohibitions of article 6 (VII) of the Biosafety Law:

- intermediate products, such as vectors and constructions (provided they meet the other requirements of the Brazilian IP Statute); and
- processes for restoring fertility based on the activation/ deactivation of genes as long as they do not involve the use of external chemical inducers.

[200] Broad process claims, involving the manipulation of fertility, which include both the production of infertile and fertile structures, must be objected based on article 6 (VII) of the Biosafety Law. It is up to the examiner to assess whether it is possible to restrict the subject matter claimed to that which does not fall under the prohibitions of the Biosafety Law.

Examples of accepted claims:

- Gene construction characterized by comprising a gene of SEQ ID NO: X whose gene expression of inhibition of fertility is active and is only inactivated with the application of an external chemical inducer.
- Expression cassette, characterized by:

a) a first male flower-specific promoter sequence of SEQ ID NO: Xoperably linked to the SEQ ID NO: Y gene, which encodes the expression of a transcription factor capable of regulating the expression of a gene operably linked to a promoter sequence of SEQ ID NO: Z, in the presence of an external chemical inducer;

b) a second promoter sequence of SEQ ID NO: Z operably linked to a restorative gene of SEQ ID NO: W encoding a product capable of restoring male fertility.

- Plant fertility restoration process characterized by activating the expression of the gene of SEQ ID NO:

X, operationally linked to the promoter sequence of SEQ ID NO: Y, subjecting the plants to a temperature between 25 and 32°C.

8 Patent applications involving components of the national genetic assets

[201] In November 2015, Law No. 13,123 came into force, which regulates the activities of access to the national genetic assets and associated traditional knowledge in Brazil, replacing the MP 2,186-16/2001. According to article 47 of Law No. 13,123/2015, "the granting of intellectual property rights by the competent body over finished product or reproductive material obtained from access to genetic assets or associated traditional knowledge is subject to registration or authorization, under the terms of this Law".

[202] Said registration of activities is mandatory (article 2, XII of Law # 13,123/2015) and must be carried out prior to the filing of the patent (article 12, § 2 of Law # 13,123/2015), under the terms of Decree # 8,772/2016 (article 20, § 1, II). When filing a patent application, the user must inform if there was access to the genetic assets or associated traditional knowledge, as well as if there is an access registration (article 109 of Decree # 8.772/2016).

[203] The registration of access activities is carried out in the National Management System for Genetic Assets and Associated Traditional Knowledge – SisGen, (http://sisgen.gov.br), and must follow the deadlines established by CGEN.

[204] The applications under processing that do not contain information on the occurrence of access may be required to submit a statement on this issue. In such cases, the applicant of the application whose subject matter results from access must present proof of registration or authorization.

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