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Examination Guidelines for Patent Applications

Biotechnology Inventions

This text is an integral part of the Patent Application Examination Guidelines setting out the current understanding of the BRPTO on Biotechnology Inventions.Other inherent exam topics are listed and discussed in the general guidelines.

Patent Division - March 12, 2015

FEDERAL CIVIL SERVICE

MINISTRY FOR DEVELOPMENT, INDUSTRY AND FOREIGN TRADE

BRAZILIAN PATENTS AND TRADEMARKS OFFICE

EXAMINATION GUIDELINES FOR PATENT APPLICATIONS BIOTECHNOLOGY INVENTIONS

RULE #144/2015

PATENT DIVISION – MARCH 12, 2015

SUMMARY

1. Biotechnology protection Requirements

The requirements of novelty and inventive step are discussed in the Examination Guidelines for Patent Application. This Annex will highlight only some specific characteristics of biotechnology patent applications.

1.1 Industrial Application

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

When the invention involves biological sequences, the industrial application requirement is met only when some utility is disclosed by the above-mentioned sequence.

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]: *SEQ ID NO: 1 protein 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 practical use for the sequence (marker for in vitro diagnosis of prostate cancer), even if its biological function is unknown.

Example[2]: *The application discloses a SEQ ID NO: 1 protein that was isolated from yeast, although it does not disclose any function/application for the protein and 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 that comprise it, are not suitable for industrial application, as these materials do not present any defined practical utility.

2. Protection Conditions

2.1 Unit of invention

A patent application must refer to a single invention or to a group of inventions so interrelated as to comprise a general single inventive concept (article 22 the Brazilian IP Statute - Statute #9,279/96; see Examination Guidelines for Patent Application, Block I).

Example[3]: *Multiple nucleic acid molecules that share a common structure and code 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 code dehydrogenases that include a conserved motif sequence defining the catalytic site. The three nucleic acids are isolated from three different sources (mouse, rat and human) and modified. The specification clearly shows that these three nucleic acids are homologous, based on their global sequence identity (85% – ¬95% identity) for both 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 Suficiency of disclosure (article 24)

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 (see Examination Guidelines for Patent Application, Block I). 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).

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).

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 skileed 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 is not a method that can be performed.

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 the characteristic is found in nature.*

Example[5]: *The application describes a new and inventive method of obtaining mutant microorganisms through random mutagenesis. As the stages 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, this 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 such outcomes.*

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 this 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 antagonist and agonist compounds. The person skilled in the art would not be able to execute 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 function. 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

Should biological material be essential for the practical implementation of the object of the application, which can not 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 (Budapest Treaty; see Examination Guidelines for Patent Application, Block I).

In this context, “biological material” may refer to any material containing genetic information and capable of self-replication (direct or indirect). Representative examples include bacteria, archaea, protozoa, virus, 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 centre, the host cell containing these biological materials may be filed.

2.2.1.1 Cases in which a Biological Material must be Filed

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 filing of the material does not necessarily apply to all and any biological material involved in a specific invention. For example, polynucleotides and polypeptides, must be described through their nucleotide and amino acid sequences (note: nevertheless, there is nothing that prevents such materials to be additionally filed).

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 filing 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 description, in order to allow a person skilled in the art to implement the invention.

In cases where the microorganisms are selected through random mutagenesis and the genetic alterations that result in a 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 filing authority, and the filed data (such as filing declaration or name of the institution, with the number and date of the filing) form part of the application (see item 2.2.1). Thus, the biological material will be available at the filing authority and shall consequently be considered as being clearly and sufficiently described, as well as repplicable. Should the microorganism not have been filed, the matter will not be in accordance with article 24 of the Brazilian IP Statute.

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 file the biological material in order to ensure that the matter complies with article 24 of the Brazilian IP Statute. On the other hand, it is not necessary to file 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 specifically to the nucleic acid to be used in this transformation, and ensuring that this nucleic acid is described in a clear and accurate manner.

In cases when 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 filing of the microorganism or the biological material shall also be necessary.

2.2.1.2 Deadlines for Filing a Biological Material

With regard to the original filing of biological material for patent purposes, Normative Instruction IN PR #17/2013 establishes that the biological material must be filed until the filing date of the patent application, and that this data must be included in the specification. Should there be a Paris Union priority, the biological material must be filed prior to or by the priority date claimed, if pertinent, in other words, if the priority rights are applicable to the biological material.

When the evidentiary data on the filing 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 Listings

The patent application whose object contains one or more nucleotide and / or amino acid sequences that are crucial for the description of the invention must 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 Application, Block I). It is stressed 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 ordering the sequences to be presented. 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.

Rule #228/09 issued by the BRPTO and included in Rule PR #81/2013 also issued by the BRPTO, governs the procedures for the presentation of the sequence listing on electronic media, replacing item 16.3 of Rule #127/97 (see Rule PR #81/2013 and the Annexes appended thereto and published in the Federal Official Gazette (DOU) – §1, #68, April 10, 2013).

2.3 Support, Clarity and Accuracy (article 25)

2.3.1 Support in the Specification

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 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 acids residues and also discloses an immunogenic fragment of this mutated protein (not natural), determined as consisting of residues 320 to 400 of the above-mentioned protein. In term, the claim chart requests protection for the immunogenic protein and for the immunogenic fragments of this protein (claim 1). However, the specification discloses only an immunogenic fragment of this 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 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 this protein.

In this example, even if the applicant presents new information on other immunogenic fragments of the above-mentioned protein that have not been described in the matter initially disclosed, this information may not be taken into consideration, as the specification did not mention other immunogenic fragments of this 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 matter in the specification.

Example[10]:

Claim 1: Process of plant transformation 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 this 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 the data must be included in the specification, which would constitute an addition of matter, thus not complying with article 32 of the Brazilian IP Statute.

3. Claims

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 Application, Block I).

In the biotechnology area, some non-exhaustive examples of subject matter considered to fall in 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 to produce a compound/composition; process for selecting a nucleic acid/polypeptides/peptides sequence; process to produce a transgenic microorganism/plant/animal; purification method; extraction/isolation processes, among others.

3.1 Reach-through Claims in Biotechnolog

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.

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

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 at 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.

Another type of reach-through claim in biotechnology is the modular compound identification process 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 this 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

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 the polypeptide in question with a compound to be traced; and (b) determining whether the compound affects the activity of the polypeptide in question. Claim 2: An agonist/antagonist characterized by being for polypeptide X as identified through the process defined in claim 1.

This 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 this process.

Claim 1 defines the main invention ofthe 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), clarity, accuracy and support (article 25). Claim 2 uses functional (rather than structural) characteristics to define the matter for which protection is requested. However, the definition of a product through functional characteristics frequently results in a lack of clarity for the matter addressed thereby. 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 at the state of the art and / or that are encompassed by the prohibitions set foth in article 10, IX.

Claim 2 requests protection for candidate compounds identified through the screening method of the invention as defined in claim 1. These compounds were technically defined only through their activity (meaning a functional definition – wording that is common to this type of claim) which in this situation corresponds to a modulation (agonist/antagonist) of the activity of polypeptide X. The structural characteristics of the candidate compounds were not defined; this 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 Matter Excluded from Protection under The IP Statute

4.1 Definitions

Pursuant to the understanding adopted by this Institute, from the technical standpoint, the terms and expressions used in this item are construed in the following manner:

- "whole" (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, as 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 worthwhile stressing that synthetic molecules that are identical to or indistinguishable from their natural counterparts are also encompassed by this definition;
- "isolated from nature" is all and any subject matter extracted and run through 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;
- "germplasma" 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 designed to cure or prevent 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.

4.2 Subject matter not considered as Inventions (article 10)

4.2.1 Natural Biological Products and Processes (Article 10 (IX)

With regard to claims in the "product" category, article 10 (IX) of the Brazilian IP Statute stipulates 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 germplasma of any natural living being.

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 to constitute inventions.

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

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 occuring 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.

Thus, the inclusion of a disclaimer with the expression “not natural” does not rebut, in itself, the objection raised grounded on article 10 (IX) of the Brazilian IP Statute.

4.2.1.1.1 Compositions containing Natural Biological Products

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

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 merely represents a mere dilution, on the bottom line (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. Consequently, 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”.

4.2.1.1.2 Extracts

Extracts are biological materials isolated from nature and are, consequently, not deemed to constitute inventions, based on article 10 (IX).

Thus, for extracts-containing compositions, the same remarks are valid as presented above for natural products.

4.2.1.1.3 Enriched Extracts

Extracts that differ from their natural counterparts through 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.

Attention must also be paid to the issue of extracts of transgenic bacteria cells. Although the microorganism per se might be patentable, this 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 1: Plant extract characterized by being enriched with isoflavones

The extract is enriched with isoflavones through 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).

Example[13]: Extract enriched through 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, this extract is open to protection.

4.2.1.2 Natural Biological Processes

"Natural biological process" means any biological process occurring spontaneously in nature and where human intervention does not affect the final outcome.

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 stage with a decisive impact on the final outcome and that might not be achieved without human intervention, are considered to constitute inventions.

Regarding this concept, the classic process of obtaining plants or animals is not an invention. Similarly, processes that encompass only stages 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.

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)).

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

Similar to other processes, biological processes claims correctly drafted define the starting material, the product obtained and the means for transforming the former into the latter; the various stages needed to attain the proposed objective or; in the case of use, the material to be used and the purpose of this use.

Examples of acceptable claims (note: the level of detailing required will depend on the specific invention under examination):

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

4.2.1.3 Use of Natural Products

When the claimed process involves the whole or part of natural living beings and biological materials found in nature, including the genome or germplasm, but does not consist of a natural biological process, there is no 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 the 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 under article 18 (I) of the Brazilian IP Statute

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

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 refuse to patent such inventions, grounded on article 18 (I) of the Brazilian IP Statute.

The following examples are non-exhaustive:

a. processes cloning human beings;
b. processes modifying the human genome that result in modifications to the genetic identity of human germinative cells; and
c. processes involving animals that cause suffering thereto, with no substantial medical benefit for human beings or animals resulting from such processes.

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 under Article 18 (III) of the Brazilian IP Statute

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.

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".

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.

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 this does, actually, refers to a microorganism that expresses a characteristic normally not attainable by the species under natural conditions.

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 occur naturally 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

The generic term "microorganism" is used for bacteria, archaea, fungus, single-cell algae not classified in the Plant Kingdom and protozoaria. 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 microorganism claims (non-exhaustive list)

- Transgenic microorganism characterized by containing the SEQ ID NO: X.
- Transgenic microorganism characterized by containing the SEQ ID NO: X inserted in the Y position of the genome.
- Transgenic microorganism characterized by containing the xxxxxxx sequence in the Y position of the genome (see item 2.2.2).

- Transgenic microorganism characterized by containing the X gene (provided that the gene is well known).
- Transgenic microorganism characterized by containing the X gene with the Z promoter inserted at 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 the ATCC-XXXX (filing number).

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

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); (ii) natural occurrence (article 10 (IX)); (iii) clarity, accuracy and support (article 25) in the manner in which such molecules / sequences are claimed; (iv) novelty (article 11); (v) inventive step (article 13); and (vi) industrial application (article 15).

The sufficiency of disclosure for bBiological sequences is addressed specifically in item 2.2.2.

The novelty requirement, when related to biological sequences, follows the same general principle (see Examination Guidelines for Patent Application, Block II), meaning that for an amino acid or nucleotide sequence not to meet 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.

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

6.1 How to Characterize

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).

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 #81/2013, 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. number of filings (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.

It is stressed that a DNA must be defined through its nucleotide sequence, while a protein must be defined through its amino acid sequence, in order to clearly define the matter presented for protection.

Moreover, attention must be paid to claims of the following types, as none of them presents clarity (article 25).

a. DNA sequence characterized by coding 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 through the amino acid sequence, which is not permitted. However, the claim may be altered in a manner that defines the DNA through the nucleotide sequence, with their degeneration being accepted, which generates the same protein. In this situation, at least one nucleotide sequence must be present in the application as filed, unless it is a sequence that is already available in the state of the art and is mentioned in the specification.
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

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

Formula 1 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.

For further details on Markush formulas, see the Examination Guidelines for Patent Application, Block II.

6.1.2 When the Sequence Listing must be Filed with the Application

Rule PR #81/2013 issued by the BRPTO 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.

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, this 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 #81/2013).

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

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 the invention out. 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 the invention out.

6.1.3 Need to limit the claim chart to the sequences filed with the application

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), this method does not necessarily need to refer to a single SEQ ID NO:, 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 such bacteria are transformed by a vector containing the sporulation gene under the control of any promoter. 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 stipulated specific 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, as this 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 through its corresponding SEQ ID NO.

6.2 Homology versus Identity

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 here.

Two sequences (of nucleotides or amino acids) are homologous only when they share a single common ancestor. Thus, 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).

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.

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. Thus, if two proteins present 90% identity, this means that 90% of all the amino acid residues in the above-mentioned proteins have identical corresponding positions.

On the other hand, the percentage of similarity between two protein sequences refers to the sum of identical and similar matches (for example, the glutamate and aspartate amino acids are considered as 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.

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

a. claim such as "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 ofarticle 25 of the Brazilian IP Statute), as, technically, the term "% homology" is not applicable, as stressed above; and
b. claim such as "DNA (or protein) sequence characterized by presenting at least 80% identity (or similarity) with SEQ ID NO: 1" can not 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 object of the protection is not clear and precise, contravening article 25 of the Brazilian IP Statute.

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 allowing 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

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 above-mentioned molecule. The following items discuss the particularities of some of these molecules.

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 Modifications of Nucleotide Sequence(s)

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 can not be accepted, as the resulting molecule would be indistinguishable from its natural counterpart, even if produced in a recombinant manner.

6.3.1.1 Modifications of sequence (s) through substitutions, insertions or deletions of non-modified nucleotides

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.

Should the nucleotides be deleted in the middle of the claimed sequence, this 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 this 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).

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

However, it must be borne in mind that assorted 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),

while the amino acid sequence encoded by this sequence remains identical to its natural counterpart, consequently falling under article 10 (IX).

When analyzing sequences derived from the state of the art that are not encompassed by article 10 (IX), 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.

6.3.1.1.1 SNPs

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

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 Protector Groups)

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). 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 a natural biological sequence.

The inclusion of these nucleotides in the sequences presented in patent applications is addressed in Rule PR #81/2013 issued by the BRPTO, 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 in Table 2 of the Annex appended to this Rule (published in the Federal Official Gazette (DOU) – §1, #68 of April 10, 2013).

6.3.2 Fragments

Special attention must 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 matter described in the application.

Exemplo[18]: *An application presents a sequence SEQ ID NO: 1 (hypothetical): agctggttcgactgtctcga. The claim refers to the "nucleic acid characterized by possessing the nucleotide sequence SEQ ID NO: 1 and fragments thereof". In the manner in which it is described, this 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 defined clearly and precisely 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.

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

6.3.3 Oligonucleotides (or Primers)

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

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.

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). On the other hand, should it present modifications that result in a nucleotide sequence that differs from those found in nature, it will not be subject to article 10 (IX) (see item 6.3.1).

Moreover, as a mixture of oligonucleotides (for example, degenerated oligonucleotides, etc.) might not be clearly and precisely defined, claims related to this 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).

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

The promoter is the central regulation processor 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 locate further away from the transcription starting point (enhancer and silencer sequences).

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.

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, this in silico analysis is not sufficient to demonstrate that the identified sequence is in fact a promoter region, adequate functional trials are required for validation.

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

The above-mentioned sequence was isolated and presents promoter activity: this 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, also be encompassed by 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 linked operationally to a gene of interest and a terminator sequence.

Should sequence 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 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, through introducing the term "heterologous", making it clear that this does not encompass protection for material falling 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 the SEQ ID NO: 1 to 3 or its fragments and derivatives linked operationally to a heterologous gene of interest and a heterologous terminator sequence.

This type of claim must be analyzed by taking into consideration the above remarks on the example. 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 promoter activity been demonstrated only for sequence SEQ ID NO: 1, for example, the claim must be limited to this sequence; furthermore the expression "or its fragments and derivatives" 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 matter might be queried, pursuant to article 24 of the Brazilian IP Statute.

6.3.5 Vectors

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 a sequence that corresponds to the 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 identified easily; 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.

With regard to sufficiency of disclosure as set forth in artincle 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, of whether the vector is the main invention or an acessory 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, the marker sequences or sequences that confer resistance to antibiotics, etc.;
- the sequence to be cloned and / or expressed in the form of SEQ ID NO: X 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 may 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.

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 filed (see item 2.2.1).

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 the expression of a gene of interest. In this case, the vector might be characterized in a claim by its filing number issued by an International Filing

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 original sequence for replication, selection marker sequence and multiple cloning sites chacacterized 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 for replication, the selection marker sequence (for antibiotics, etc.) and the restriction enzyme sites. Consequently, the essential elements that distinguish this 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 an inter-related invention

Claim: Vector characterized by ***comprising*** of the sequences defined by SEQ ID NO: X and SEQ ID NO: Y linked in an operative manner to the promoter and terminator heterologous sequences.

The invention describes two gene sequences involved in the transport of lysine that were isolated from Corynebacterium glutamicum. Sequence SEQ ID NO: X codes the lysine exporter protein (LysE), while sequence SEQ ID NO: Y codes 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 is not encompassed by the provisions set forth in article 10 (IX) of the Brazilian IP Statute.

Example[25]: Vector as an 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 constructions as a whole presents some heterologous sequence as a way of distinguishing it from the natural sequence. Consequently, if sequence SEQ ID NO: X is altered, the term "heterologous", as used in example 24 is not necessary.

6.3.6 cDNA

cDNA molecules represent sequences produced through 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 this 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.

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

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).

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 Expressed sequence tags - ESTs

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).

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.

Furthermore, in order to avoid falling under article 10 (IX), an analysis of this subjet matter follows the same criteria used for cDNA; whereby it is necessary to know if the above-mentioned EST represents a sequence fragment 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).

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 Open reading frames - ORFs

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

As this 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).

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 demonstrate the functionality of the product obtained through the expression of this ORF in order to comply with the industrial application requirement (article 15), as well as the clarity and accuracy of the claimed matter (article. 25).

6.3.9 RNAs

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.

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 may not be considered as natural biological material.

6.4 Amino Acid Sequences

For the purposes of definition, when analyzing patent applications, “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 Resolution PR #81/2013). Consequently, the mention of 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 characterized Amino Acid Sequences

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 chartmust refer to the proteins in question through the SEQ ID NO: in some cases, additionally, this may also correspond to their structural formulas. Sequences with up to 3 (three) amino acid residues must be represented throughout the entire application only by its sequence.

Exemplo[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 SEQ ID NO: 1 sequence.

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 this situation, a requirement must be issued, for the applicant to submit the amino acid sequence corresponding to the nucleotide sequence presented, without this constituting any addition of matter.

Thus, claims will not be accepted with the protein sequences characterized only through their properties, such as three-dimensional structure, biological activity, name, chemical properties (PI, molecular weight, amino acid composition, etc.), as the only way of defining an amino acid sequence clearly, precisely and unmistakably is through the sequence itself.

Furthermore, attention must be given to item 6.2 of these Guidelines, which addresses biological sequence claims through the percentages of identity and / or similarity to a reference sequence.

It must 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 sequence SEQ ID NO: W. In this case, it would not be possible to accept a generic claim requesting protection for a mutated (not natural) protein that is characterized by comprising the sequence SEQ ID NO: W, as this would introduce the possibility of any extension in the carboxy and / or terminal amino 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 sequence will function similarly to the protein that consists of the SEQ ID NO: W sequence, 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 attain the same results.*

6.4.2 Homologous Proteins (Paralogous versus Orthologous)

Homologous proteins are proteins derived from a "common evolutionary ancestor". They may be present in a single species, deriving from gene duplication, originating in 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.

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. This protein B presents a sequence and activity 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. Nevertheless, in this case, protein B would not be considered as constituting an invention under article 10 (IX).*

Moreover, when applications involve "variants" or "modifications" of natural proteins, attention must be paid to the scope of article 10 (IX), as such modifications may result in another biological molecule that is proven to be natural, deriving merely from a species other than that 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 this protein, which is already known. In this case, even if 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 is consequently also subject to article 10 (IX).*

6.4.3 Protein Fragments

Similar to a protein, a protein fragment must be characterized by at least its amino acid sequence (see item 6.4.1). Thus, when a protein fragment is claimed and characterized only through its linear sequence, the examiner must conduct a search for the characterizing amino acid sequence. Should the sequence be found at 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.

When a peptide containing a few 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 material 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 Statute 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.

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 for the state of the art, as it constitutes part of a natural living being or a biological material found in nature, this does not constitute an invention under article 10 (IX) of the Brazilian IP Statute, thus not warranting any type of analysis of its novelty and inventive step.

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.

Thus, 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 having the Ile-Leu-Arg sequence

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 twisting, spacial conformation, aggregation and physical and 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 material 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 of 76 amino acids when truncated at the sixth amino acid amino terminal, began to exhibit an antagonist activity for the entire cytokine, and thus might be used to manufacture medicines for treating diseases that require a cytokine antagonist.

Although human interference produced results in an innovative activity, this fact occurred merely through 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, this analogue is not considered as constituting an invention as it consists of part of a natural molecule, and is thus not patentable.

6.4.4 Modifications to the Sequence

Modifications of protein sequences intended to distinguish them from natural sequences may be handled 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 this does not fall under article 10 (IX) of the Brazilian IP Statute.

6.4.4.1 With Natural Amino Acids (Substitutions, Insertions or Deletions)

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

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

With regard to the substitution of amino acids by other natural amino acids, this 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).

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 Protector Groups)

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). 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, to result in the natural biological sequence.

The inclusion of these amino acids in sequences presented in patent applications is also addressed in Resolution PR #81/2013 issued by the BRPTO, as mentioned in item 2.2.2 of these Guidelines; and a list with examples of non-natural amino acids and the acronyms that are acceptable for their definition is available in Table 4 of the Annex appended to this Rule (published in the Federal Government Gazette (DOU) – §1, #68, April 10, 2013).

6.4.4.3 Groupings added to the terminal carboxy or amino

A protein sequence might also be altered through binding chemical groups to its ends, in order to allow it to be

anchored to a specific surface or structure, with increased protein activity, bio-availability modulation and / or circulating half life, etc.

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 this 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

By definition, these are proteins created by the union (fusion) of the parts of two or more different protein sequences. Thus, a fusion protein addressed by a patent application is formed by at least a "functional" portion that accounts for the property related to the invention.

Consequently, for the purposes of definition and in compliance with article 25, 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

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.

Once the occurrence of a natural identical structure has been proven, consoant with 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

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 must be referred through at least by one of their amino acid sequences or by the SEQ ID NO: corresponding to the functional portion.

6.4.5.3 Entire SEQ ID

When the polypeptide sequence described in the patent application is claimed in the form of a fusion protein, this must always be referred through 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.

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 referred through at least their amino acid sequence or the corresponding SEQ ID NO:.

Special attention must be paid to cases in which the “fusion” protein is in fact formed by fragments of a same protein that occur 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 that consists 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 that consists of the 69-84 amino acid sequence of SEQ ID NO: 2;
d. a second spacer of 5-11 amino acid; and
e. a third polypeptide that consists of the amino acid sequence 92-105 of SEQ ID NO: 2.

In this claim, as there is no definition of the spacers of interest, 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 sequence SEQ ID NO: 2, which occurs naturally, falling under article 10 (IX).

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

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

An application might, 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 this might be fused to several others.

Example[34]:

The application describes a polypeptide X that alone 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 in 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 efficacious 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 as required 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 tothe 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

Antibodies are plasma proteins that bind specifically to known substances such as antigens, and include polyclonals and monoclonals; consequently, they must be analyzed as proteins, including in regards to the provisions set forth in article 10 (IX) (see item 6.4 and its sub-items).

Polyclonal antibodies are derived from different B cell lines. They are a mixture of immunoglobulin molecules secreted against a specific antigen, with each recognizing a different epitope. These antibodies are biological products isolated from nature and, thus, are not considered to constitute inventions under the provisions set forth in article 10 (IX) of the Brazilian IP Statute. It is worthwhile stressing that the isolation of a specific antibody from this pool of antibodies does not exclude this molecule from the condition set forth in article 10 (IX).

Monoclonal antibodies are antibodies with a single specificity, meaning that they are specific for a single epitope in an antigen. Through human intervention, a monoclonal antibody can be obtained by different techniques, such as hybridoma (see item 6.4.6.2) or genetic engineering techniques.

When obtained through a hybridoma and characterized as such, a monoclonal antibody might not be considered natural and would, consequently, not be subject to the provisions set forth in article 10 (IX). It must be stressed that, in this situation, this monoclonal antibody might additionally be defined by its specific sequence (SEQ ID NO:). For monoclonal antibodies obtained through genetic engineering, as they are defined by their sequence they may be accepted, provided that they are not subject to the provisions set forth in article 10 (IX) (see item 4.2.1).

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, filed under number YYYY.

Example[36]: Antibody claims that are not acceptable.

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

As they do not clearly and precisely define the antibodies that are being claimed, such claims cannot be accepted as they contravene article 25 of the Brazilian IP Statute, and may encompass natural molecules, including those addressed in article 10 (IX).

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

Claim 3: Monoclonal antibody and its fragments characterized by the fact that it can bind to protein X.

As they fail to define the antibodies clearly and precisely, not stating which fragments are being claimed, these claims may not be accepted, as they contravene article 25 of the Brazilian IP Statute.

6.4.6.1 Process of Obtaining Antibodies

The production process for a polyclonal antibody that consists only of the exposure of an animal to an antigen, followed by purification, is considered a natural biological process, and is thus not deemed to constitute an invention, falling under article 10 (IX). However, in some cases, if any non-trivial technical stage involving the determination of the epitope or modification of the antigen in order to elicit the immunological response, it is felt that there is significant human intervention, given that there is a direct action on the molecule, with a decisive impact on the final results. In these cases, such processes are liable of patent protection.

In counterpart, due to human intervention, the production process for monoclonal antibodies is not considered to be a natural biological process, whether this involves obtaining it through a hybridoma or through genetic engineering techniques.

With regard to the characterization of the process for obtaining antibodies, attention must be paid to the need to define the stages of the process (see item 4.2.1.2).

6.4.6.2 Hybridomas

Hybridomas are the result of a fusion of two cell types, a myeloma and a B lymphocyte, 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 Institute, from the technical point of view, a hybridoma is considered to constitute a transgenic microorganism, and such matter is thus patentable, as it does not fall under articles 10 and 18 of the Brazilian IP Statute.

At the same time, as this involves biological material that is essential for the practical embodiment of the purpose of the patent application, and that 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, it is essential the filling of the hybridoma by the filing date of the patent application or its priority date, with the presentation of the filing number in the patent application (see item 2.2.1).

6.4.6.3 Chimeric/humanized Antibodies

Monoclonal antibodies produced from mice, rabbits, etc. when used as therapeutic agents in human beings, are recognized as foreign proteins by the immune system of the human host. The advent of chimeric/humanized antibodies is a mechanism used to surmount this therapeutic obstacle.

The technology for the production of a humanized antibody differs from the production of a monoclonalantibody, because it does not depend on cultivating the hybrid cell, but requires the immunoglobulin sequence to be obtained (human Fc portion and variable portion of the non-human Fab fragment). These sequences are merged and placed in an expression vector for subsequent cultivation of the transfected host cell and subsequent purification stages. Due to this difference in the production route, the characterization of the humanized antibody

requires the presentation of a SEQ ID NO: X containing the amino acid sequence of the variable portion of the antibody and the definition of the other elements (Fc portion).

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 the sequence SEQ ID NO: X and regions constants in the human γ chain.

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

6.4.6.4 Antibody Fragments

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 under article 10 (IX) of the Brazilian IP Statute (see item 6.4.3).

Modifications to antibody fragments may also be liable of patent protection, as is the case with single chain variables 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, meaning that the VH and VL domains may be linked by a connector, creating a single chain Fv fragment. Despite being an antibody fragment, this 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 Obtainment Processes

7.1 Animals, Plants and their Parts

If natural or isolated, they are not considered to constitute inventions, under article 10 (IX). When resulting from genetic manipulation by human beings, they are not liable of patent under article 18 (III).

7.1.1 Products and Processes involving Stem Cells

Stem cells are undifferentiated cells (totipotent, pluripotent or progenitor) that can be stimulated to differentiate into the various tissues that constitute the human body.

According to these Guidelines, products and processes involving stem cells refer exclusively to pluripotent or progenitor stem cells. These cells may be directly obtained from various tissues in the adult organism (such as bone marrow or adipose tissue, for example), or even from the umbilical cord, or they may be obtained through the dedifferentiation of a differentiated adult cell (as with induced pluripotent stem cells - IPS).

Alternatively, they may be obtained from the internal mass of blastocysts taken from human embryos produced through in vitro fertilization, pursuant to the provisions of article 5 of the Biosecurity Statute (Statute #11,105/2005), dated May 11, 2005.

According to the Brazilian IP Statute, cells obtained directly from an animal or with some modification to its genes, are not patentable under the provisions set forth in article 10 (IX) or 18 (III), respectively. However, compositions containing these cells or processes for obtaining stem cells and the application (use) thereof may be considered as patentable, provided that they do not imply or include the therapeutic and/or surgical method (article 10 (VIII)), and provided that they do not fall under the provisions set forth in article18 (I) of the Brazilian IP Statute.

For example, the following products and processes involving stem cells could be considered as liable of patent protection:

- Compositions containing cells and other ingredients (assorted implants containing cells, cell and matrix formulations, growth factors and cells...).
- Composition containing mixtures of different types of stem cells.
- Purification, preparation, conditioning, differentiation and dedifferentiation processes, or any stem cells processing that is performed in vitro.
- Uses of cells for preparing medications to treat disease X.
- Uses of cells for preparing implants to treat disease X.
- Uses of cells for preparing compositions to diagnose disease X.
- Diagnostic processes that include stages using stem cells or synthetic tissues, provided that they are performed in vitro.
- Drug tests that include stages using stem cells or synthetic tissues provided that they are performed in vitro.
- Stem cells cultivation processes.
- Conditioned culture media obtained during stem cultivation.

7.2 Transgenic Plants, their Parts and Obtainment Processes

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

Transgenic plants and their parts (for example, transgenic cell, transgenic tissue and transgenic organ) are not considered as constituting patentable subject matter under article 18 (III and Sole ¶) of the Brazilian IP Statute.

Even if the process of obtaining transgenic plants is patentable, it is important to stress that the intermediate and/or final product resulting from this process, meaning the transgenic plant and/or the parts of this plant constitute materials whose patentability is expressly forbidden under article 18 (III and Sole ¶) of the Brazilian IP Statute. However, there are no constraints on patenting the processes used for obtaining these plants.

Examples of Claims Liable of Patent Protection

Production method for transgenic plant characterized by comprising the following stages:

a. obtaining a plant explant;
b. exposure of the explant to a culture of Agrobacterium tumefaciens that contains the vector defined in claim X (duly described with a selection gene, a heterologue gene and the promoter sequence(s);
c. cultivation of the explant in a medium with the specific cultivation conditions required for vegetal tissue; and

d. selection and cultivation of the transformed callus expressing the heterologous gene, in order to induce the formation of an embryonic callus.

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

a. transform plant cells using an Agrobacterium transformation vector that comprises a chimeric construct of gene Y;
b. obtain a transformed plant cell; and
c. regenerate a genetically modified plant from the transformed plant cell.

7.3 Process of Plant Obtention Through Crossing

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.

"Natural biological processes" is taken to mean 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. Along these lines, biological processes shall be considered as not natural when direct human intervention is required in the gene composition, and the effect is permanent.

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

Example[38]: Non-transgenic parentals.

Claim 1: Methods for producing a plant X characterized by comprising the following stages:

a. selection of a plant X homozygote for gene A;
b. selection of a plant X homozygote for gene B; and
c. crossing the selected plants at stages (a) and (b) in order to produce a hybrid plant.

Conventional methods of producing plants based on stages of selection, crossing and propagation, are considered to be natural biological processes, falling under article 10 (IX). In these cases, human intervention through the selection and induction of specific crossings is not essential for the process to occur, but merely speeds up or limits what would occur in nature.

Example[39]: Non-transgenic parentals.

Claim 1: Method for producing a plant X with high levels of compounds W, characterized by comprising the following stages:

a. identifying gene markers linked to high levels of W;
b. selecting individuals through the markers identified in stage (a); and
c. crossing the selected individuals in stage (b).

Conventional plant production methods based on stages of selection, crossing and propagation in which human intervention consists of merely providing additional technical procedures to streamline or steer the process propagation - in this case, the identification of gene markers - are considered as natural biological processes falling under article 10 (IX). In these cases, human intervention is not decisive for obtaining the final result, merely speeding up or limiting what would occur naturally.

Example[40]: Transgenic parentals.

Claim 1: Method of producing hybrid seeds characterized by comprising the crossing of a herbicide resistant plant with a plant endowed with enhanced nutritional value comprising in its genome a heterologue gene coding for a modified albumin.

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

a. crossing a plant resistant to at least one herbicide with a plant whose genome encompasses a heterologue gene coding a modified albumin;
b. developing background populations;
c. assessing plants obtained individually; and
d. selecting plants with enhanced nutritional value encompassing the characteristic of resistance to herbicides.

This process involves a technical stage that is essential for obtaining the plant that does not occur in nature, and consequently does not fall under article 10 (IX).

8. Patent Applications involving Genetic Heritage Components

Patent applications of inventions for a process or product obtained through samples of components in the Brazilian genetic heritage, filed as of June 30, 2000, must comply with the standards established in Provisional Measure (MP) #2186-16/01 promulgated on August 23, 2001, as well as Rule #34 by CGEN on February 12, 2009 and Rule PR #69/2013, issued by the BRPTO on March 18, 2013.

Provisional Measure (MP) #2186-16/01 rules, among other matters, on the assets, rights and obligations arising from access to a component of Brazil's genetic heritage found in Brazilian territory, on the mainland and in the exclusive economic zone for the purposes of scientific research, technological development or bioprospecting, as well as access to traditional knowledge associated with the genetic heritage that is relevant for conserving biodiversity, the integrity of Brazil's genetic heritage and the use of its components (article 1, items I and II).

In its article 31, this Provisional Measure states that the granting of industrial property rights for a process or product obtained through a sample of a component in the genetic heritage is conditional on compliance with the Provisional Measure (MP), with the applicant necessarily stating the origin of this genetic material and the associated traditional knowledge, when applicable.

The standards established in Provisional Measure (MP) #2186-16/01 must be complied with in patent applications involving Brazil's genetic heritage. As non-exhaustive examples, organisms may be mentioned (plants, animals, fungus, bacteria, archeae, etc.), parts of organisms (leaves, claws, skin, mucus, blood, roots, extracts, organs, oils,

poisons, fangs, etc.), molecules isolated from organism (DNA, RNA, proteins, sugars, lipids, etc.), and their synthetic correspondent, as well as compositions and processes containing any one of the above-mentioned items. Pursuant to article 3, this Provisional Measure (MP) is not applicable to human genetic heritage.

The applicant must always provide information on the origin of the material through the petitions established in Rule PR #69/2013 issued by the BRPTO: a petition requesting information on access or a petition to declare that the application filed does not involve access as addressed in Provisional Measure (MP) #2186-16/01. Pursuant to Rule #35/2011 issued by the CGEN, for regularization purposes, the registered request for authorization to access the genetic resource may be accepted, with the allowance of the patent application being conditional on presentation of the definitive authorization to access the genetic resource.

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