R E P O R T

On the patentability of biotechnological inventions

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INTRODUCTION

The present report concerns one of the most topical problems in bioethics with major practical implications. The rapid development of genetics and biotechnology is directly linked to the parameters of modern economy.

On the one hand, this development is based on broad strategies of highly expensive research with a large degree of uncertainty as to the outcome for it is innovative research in largely unknown fields.

On the other hand, the achievements are often of big economic interest, again because of the innovations they bring to significant areas of goods and services as, for instance, in agriculture and animal breeding, medicine and pharmaceuticals, in particular.

It is now commonplace that biotechnology represents one of the most attractive sectors of modern economy promising high returns for those who act in time on the market and are willing to assume the relevant risks.

This increasing interdependence between biotechnology and the economy has drawn attention to the issue of protection of biotechnological inventions. The starting question is simple: may those who invest resources and scientific work of a high failure risk in pursuit of a biotechnological breakthrough be the only ones to benefit from it by legally barring access of third parties to it?

In the context of modern legal systems, this question is part of the wider issue of "intellectual property" rights, namely rights that safeguard various products of the mind. In particular, it seems to belong to the scope of patents, i.e. rights conferred for all sorts of "inventions".

The reflexion on the patentability of biotechnological inventions revolves precisely around the scope of patentability. For these inventions involve interventions in the

process of living and not in the inorganic world as it happens with other technological inventions.

Two major questions arise here: a) can the isolation of elements found in living systems (e.g. specific genes, DNA sequences, cells, tissues, organs, etc.) be literally considered "invention" so that we may properly speak of "patent" rights in the strict legal sense of the term? b) is it morally acceptable to confer exclusive rights on living organisms or on living in general?

These two questions will be discussed as thoroughly as possible with a view to systemizing reflexion (1). After what some examples of biotechnological inventions involving plants, animals or human beings that have been patented will be described (2). Next, we will present the legal aspects as emanating from international, EU and foreign law and, with more detail, as stipulated by Greek law (3). Finally, based on the above, we will attempt to outline some directions for bioethics (4).

1. GENERAL TOPICS

1. The object of any patent is "invention". This general premise is not put in question by modern law, at least not for the time being. The aim of this characterization is to exclude in principle the patentability of simple "discoveries" of real world phenomena that are accessible to any observer.

In particular, for an invention to be patentable it must:

a) be *novel*,
b) involve *inventive activity*, and,
c) be prone to *industrial application.*

The first two elements are present when the invention is not part of the "state of the art", i.e. the set of written or oral knowledge that is available internationally, or does not obviously result from it. The third condition is met when the object of the invention can be produced or used in any sector of productive activity. Naturally, the activity in question must be legitimate.

The object of patent is either a *"product"* or a *"method"* leading to production of a product. In the first case, the rightholder enjoys better protection since by obtaining a patent for the product, any method for its production is also secured. In the second case, in contrast, different method/s eventually leading to the same product are left outside the scope of protection.

On certain occasions, a specific *"use"* of an invention is also considered patentable[1]. In fact, "use" patents are a sub-group of "product" patents.

In the current context, biotechnological inventions consist of either the artificial isolation of elements (e.g. genes) or the artificial creation of living forms (e.g. bacteria or transgenic organisms). The "products" of these inventions – that is, the elements that are isolated or the organisms that are "fabricated" for the first time in a lab – are unquestionably "living".

The reasonable question that emerges is the following: *given that life as physical phenomenon exists and does not spring out of nothing can such partial aspects of living be considered "inventions" – and not mere "discoveries" – so that they may be patentable* in accordance with the above?

2. In addition, there is a deeper reflexion irrespective of whether the characterization of biotechnology applications as "inventions" or "discoveries" is pertinent or not from the legal-technical point of view.

It is generally accepted in legal doctrine and practice that patents confer to rightholders the right to:

a) exploit the specific invention in terms of production for a certain period of time for personal benefit, and,
b) forbid third parties to exploit the same invention during that time[2].

Without overlooking the ethical-social significance of the institution of patent, is it justified that this strong form of control by the patent holder over his invention be extended to any object or technique or should some exceptions be accepted in consideration of other – eventually more important – socioethical values? What is presented with here is a matter for balancing values.

The institution of patent reflects two values of modern civilization expressly enshrined in international instruments and Constitutions. It concerns, on the one hand,

[1] See, for example, UNESCO, Intellectual Property in the Field of the Human Genome, Paris 2000, p. 3.

[2] The right in question ("right to patent") comes into existence *after* the responsible authority has awarded the title, i.e. the patent. Some argue that it should be distinguished from the simple – and logically preceding in time – "right of property of invention" which is acquired as soon as the inventive idea is incorporated. This initial property right includes, *inter alia*, the faculty of the rightholder to claim a patent in order to enjoy the stronger protection afforded by the main right. See Liakopoulos Th., *Commercial Law Topics III. Patent and Intellectual Property*. Ed. P.N. Sakkoulas, Athens 2997, pp. 66 sqq.

protection of property in the wider sense of the term including various versions of *intellectual property* and, on the other hand, *freedom of research*.

Patents constitute a significant aspect of enjoyment of property rights[3] since by granting exclusive benefits from the invention to the rightholder they operate as incentives for the unhindered development of economic activities. Besides, the stimulus represented by the secure productive utilization of a future invention boosts freedom of research by orienting resources and know-how also to fields involving a high failure risk.

Some stretch the moral justification of patents a little further by adding a third social aspect to these two fundamental freedoms: by making a specific rightholder – natural person or legal entity – the exclusive beneficiary of an invention, the responsibility for its real consumptive or other value becomes more visible and leaves less room for arbitrary behaviour on the market.

On the other hand, however, biotechnology, in particular, involves other important values that should also be taken into account. *Respect for human value* which by definition excludes any form of exploitation of human beings (for instance, commercialization) would seem incompatible with patenting elements of the human organism.

Protection of the natural environment and the ensuing *preservation of biodiversity* is another value that may come in conflict with patentability. Can elements of the organism of other species or entire organisms (microorganisms, plants or animals) become the object of patents? Would this not encourage a concept of "ownership of nature" with potential negative implications for, a) the normal evolution of the species and the protection of biodiversity from violent intervention – by way of exploiting patents – prone to lead to ecological disaster in the long run, or, b) the free enjoyment of the natural environment by everybody, especially by populations who earn their living from the traditional agricultural exploitation of species attracting the interests of biotechnology?

Another objection emerges from *social protection of healthcare*. Biotechnological inventions often aim at developing preventive and therapeutic techniques for

[3] In European law, the right to property covers intellectual property in general and, by implication, the right to patent as well (art. 1, ECHR, Additional Protoc., art. 17 par. 2, EU Charter). See explanatory text to the Charter by Papadimitriou G., *Charter of Fundamental Rights. A landmark in the institutional maturity of the European Union*. Ed. Papazisses, Athens 2001, p. 58-59.

drastically treating serious diseases. In this sense, they are interesting to society as a whole. If, however, healthcare is a social good and its protection is a universal value, the exclusive exploitation of biotechnology achievements in biomedicine could limit their benefits mainly to the developed world. Fatally, this would deprive of these advances developing regions predominantly afflicted by such diseases.

In addition, objections to the patentability of biotechnology arise also from *specific rights*. From the freedom of farmers, for instance, to the extent that patenting a variety of a genetically modified plant affects the so called "producer privilege", namely the possibility to use freely the seeds of the plant for a new crop. Moreover, the very freedom of research is at stake to the degree that the patenting and exclusive exploitation of biotechnological methods or products hinders free circulation of scientific information and know-how among laboratories and researchers, an aspect of crucial significance in advanced research fields.

2. BIOTECHNOLOGY – DEVELOPMENT AND APPLICATIONS

To facilitate the discussion in the Committee we decided to review the basic principles and concepts of molecular biology which were the basis for the development of biotechnology (I). Next we selected a few examples of biotechnology applications that are covered by patents or for which claims are pending (II). Our aim is, first, to demonstrate that the scope of applications covers every living matter and, second, to present certain biotechnological inventions that sparked or are still source of social controversy.

I. The development of biotechnology

In the last fifty years, from the discovery of DNA structure, gigantic insights were gained into the organization and function of genes.

Each gene corresponds to a DNA sequence and occupies a unique location in one of the organism's chromosomes. Genes produce proteins necessary to the function of the organism.

When a gene becomes active we say that it "is *expressed*". Expression is coordinated by other DNA sequences such as *promoters* and *enhancers*. When a gene is expressed what happens is that the double helix of the DNA unwinds and one of the two strands

is *transcribed* in a chain of messenger RNA (mRNA)[4]. Next, the mRNA moves on to ribosomes, special cellular organelles where the message of the mRNA is *translated* into proteins.

The uniqueness of DNA consists in that it is the only autonomous molecule, i.e. it has the ability to copy itself or, as we say, *replicate*. The transcription of DNA into RNA can be reversed in the presence of the enzyme "reverse transcriptase" and from RNA we may obtain DNA. In this case, the fabricated DNA corresponds to those sections of the DNA's double helix which code for proteins. Thus, the reaction of DNA transcription into RNA and vice versa is a bi-directional process whereas the translation of mRNA into protein is a one-way process.

Restriction enzymes and gene cloning

In the '70's, it became possible to cut DNA by way of biochemical "scissors". Enzymes, that is. These enzymes were isolated from bacteria and seem able to recognize DNA molecules entering into bacterial cells and restrict them, namely destroy them. That is why they are called restriction enzymes. Restriction enzymes are divided in groups depending on the number and type of bases they are able to recognize in a DNA sequence.

Depending on the frequency of the sequence they are able to recognize in the DNA, they can cut it in more or less segments. Hundreds of restriction enzymes have been identified and combined in order to cut DNA in segments of varying size. In fact, restriction enzymes often leave "tails" on the double helix of the DNA when they "cut" it and this made possible to "paste" DNA segments with complementary "tails".

It was discovered, in addition, that the resistance of certain bacteria to antibiotics is due to the presence (and expression) of resistance genes located not in the bacterial chromosome but in other autonomous circular DNA molecules within the bacterial cell, called *plasmids*.

By using the appropriate restriction enzymes it is possible to cut a plasmid into one or more segments. If it occurs in a single location the circular molecule is transformed into linearised DNA. Then, the linearised plasmid DNA can be stuck onto another DNA segment (e.g. a gene) by appropriate "cut and paste" manipulations to create a

[4] DNA is comprised of the bases A (adenine), T (thiamine), G (guanine) and C (cytokine); when transferred, RNA has U (uracil) in place of thiamine.

new circular chimeric molecule. When inserted in bacteria, this modified plasmid is multiplied with each cellular division of the bacteria and, since bacteria propagate fast, copies of the modified plasmid are also multiplied by the hundreds. Thus, the gene and its properties are transmitted to the next generations of bacteria. As we say, the gene is cloned and the plasmid is the cloning vector.

In general, each autonomous DNA molecule (e.g. plasmids, the genetic material of certain viruses such as the bacteriophages) but also each synthetic DNA molecule able to replicate its DNA is called vector. The union of a vector with a DNA segment is called "recombinant DNA".

Genomic libraries

The possibility to cut an organism's genomic DNA with restriction enzymes and to clone these sequences in special vectors permitted the establishment of the so-called genomic libraries. Genomic libraries are random aggregations of cloned DNA segments of an organism's entire DNA whereby each cloned part can be kept apart (for instance, in bacteria). This facilitates the study of individual cloned DNA segments.

Also, the possibility to isolate an organism's chromosomes according to size, cut them with restriction enzymes and clone segments of chromosomes led to separate specialized genomic libraries for each chromosome. This is particularly helpful for the isolation and characterization of genes whose location on the genome is known.

Another type of libraries are the cDNA libraries. Copy DNA (cDNA) is formed by the transcription of RNA into DNA in the presence of the enzyme of reverse transcriptase. Since this DNA comes from RNA, it corresponds to a gene which is expressed. As we know not all the genes of a given organism are expressed in all its organs and tissues nor are the same genes expressed in the same tissues or organs in all development stages. In order to identify which genes are expressed in various tissues and organs and various stages of development, RNA is isolated from these tissues at the stage of interest, it is transcribed in cDNA in the presence of the enzyme of reverse transcriptase and then cDNA is cloned in vectors.

Genomic and cDNA libraries are a tool and a means to study the genome for researchers. Exploring and organizing the information contained in these banks is the central aim of genome projects for various organisms.

Bioinformatics

The variety and abundance of data collected from the genome projects during the '90's led to the establishment of public (for the most part) electronic databases. The need to manage and, mainly, process this data stimulated the development of bioinformatics. Namely specialized, appropriately designed software to identify similarities or resemblances between this multitude of data. In this way it is possible, for instance, to identify DNA sequences potentially corresponding to genes, promoters, enhancers, etc.

Although most of the time the particular sequences have to be studied more thoroughly to confirm that they do constitute genes, the researchers who identify the sequences are often others than those who isolated them and placed them in the database.

The advances and developments of bioinformatics were accompanied by a rocketing increase in the number of patent claims for DNA sequences. Typically, the NGO GeneWatch UK research project that was completed few years ago (November 2000) recorded that patents were being sought for approximately 9.500 human genes and registered approximately 1.500 claims for mice genes, 500 on poultry genes and 150 on rice genes. These numbers, of only indicative value today, demonstrate the enormous economic interest represented by various genome projects, on the one hand, and the supporting role of bioinformatics in that direction, on the other hand.

Genetic modification

DNA cloning in plasmid vectors and its insertion in bacteria is a form of genetic modification of (micro)organisms. Later it became possible to integrate DNA segments (genes or synthetic DNA) in plant or animal cells in lab cultures. Genetic modification found a multitude of applications in plants where the entire organism can be obtained from a single initial cell by asexual reproduction. In relatively recent times, it was observed that genetic modification of differentiated cells combined with the method of somatic cell nuclear transfer (SCNT) can be used as a means to integrate genetic modifications in higher organisms.

If the inserted DNA correspond to genes, the genetic modification results in the inserted gene producing the same protein it produced in the original organism. When the gene transfer takes place between remote taxonomical species, i.e. when it could not have happened in normal circumstances, we speak of transgenic organisms. The term genetic modification, however, is far wider and covers the integration of any modification whatsoever into the genome of a cell or an organism. For example, it may be limited to integrating synthetic DNA able to recognize specific genes or gene products and block them thus inactivating the respective genes or their products.
The purpose of integrating a genetic modification into a cell culture or an organism by one of the methods we are going to describe may be purely investigative or used on applications from previous research. We thought it would be useful to present the basic techniques of genetic modification for which patents were obtained not only for their biological or technological interest but mainly because they demonstrate that the scope of applications spreads over the entire living matter.

1. The *Agrobacterium* method

The disease of vegetal neoplasia called crown gall is caused by the infection of (wounded) plant tissues by the soil bacterium *Agrobacterium tumefaciens*. To be more precise, it is caused by the presence of the Ti (Tumor inducing) plasmid found in the cells of *Agrobacterium tumefaciens*.
The infection and proliferation mechanism is mainly coordinated by genes located in the circular DNA molecule of the Ti plasmid. In particular, studies on the properties and behaviour of Ti plasmid showed that different regions of the plasmid DNA control different functions. Thus, the region T-DNA was identified as responsible for the neoplasia. This region contains oncogenes and is flanked by the same repetitive sequence operating as signal for the transfer of the entire region into the nuclear DNA of the plant cell. The transfer is coordinated by another region of the plasmid called conjugal transfer region. It contains genes encoding a system of proteins guiding the T-DNA region into the nucleus of the affected cell. A third region of the plasmid, the so-called toxicity region, contains genes coding for the majority of proteins required for infecting the plant cell. The infection takes place through a channel opened between the bacterial and the vegetal cell. The protein complex required for channel formation is encoded both by bacterial and plasmid genes.

Due to the cancerous nature of the crown gall cells they propagate autonomously without a specific organization model (type of cell or tissue). Therefore, two basic artificial modifications had to be introduced in the plasmid for the *Agrobacterium* system to perform the genetic cell modification required to yield entire plants. The first consists in deleting the oncogenes from the T-DNA region and the second in inserting other genes in their place. In this way, the natural transfer system of the plasmid T-DNA region remains intact whereas the transferred region is modified.
The successful application of this modified *Agrobacterium* system was patented. Two important technical characteristics of this system are that only one copy of the inserted T-DNA is usually traced in each modified plant cell and that it can be successfully applied in dicotyledonous (e.g. vegetables, tobacco) but not in monocotyledonous plants (e.g. cereals).

2. The ballistic method

The ballistic method was developed mainly as an alternative method of genetic modification especially for monocotyledonous plants where the *Agrobacterium* method is ineffective. The principle of the ballistic method for gene transfer has as follows: gold or tungsten particles are linked with vectors of "bare" DNA[5] under appropriate conditions of co-precipitation and then accelerated in different ways[6] to achieve satisfactory penetration of the coated particles across the cellular wall into the cytoplasm and the nucleus. The success rates of nuclear integration vary from plant to plant and depend on the type of tissue or organ involved, the stage of cell cycle of bombarded cells and DNA concentration in the encrusted particles.
With the ballistic method, varying numbers of copies are traced in each modified plant cell and it "works" both with monocotyledonous plants as well as with animal cells.

3. Microinjection of "bare" DNA

The microinjection technique was developed and applied predominantly in animals. The basic idea has as follows: After fertilization but before the two nuclei of egg and

[5] Like, for instance, linearised segments of plasmid DNA incorporating a gene.
[6] For example gas pulses, high voltage electric charge or even gunpowder.

sperm are coupled, the nucleus of the egg or of the sperm is injected with a solution containing a big number of plasmids (1000-20000) in which the desired gene was cloned together with DNA sequences coordinating its expression. The successful integration of at least one plasmid into the nuclear DNA of the egg or of the sperm will result in the subsequent zygote integrating the newly inserted gene in its genome. Usually, several copies of the inserted gene are traced.

4. Method of transposable elements

Transposable elements, found in the genome of most organisms, correspond to DNA sequences that can move from one chromosomal location to another. Most transposable elements are flanked by inverted terminal repeats recognized by the enzyme transposase. When the transposable elements contain the gene coding for this enzyme they are characterized as active whereas when they themselves do not produce the enzyme involved in their transposition from one location to another they are called inactive. Inactive transposable elements transpose only in the presence of active transposable elements in the genome. Transposable elements have been isolated in several organisms and used as vectors to integrate genes.

The first and more well-known transposable elements to have been isolated are the P elements of *Drosophila melanogaster* which were successfully used to transfer genes in kindred *drosophila* species. The basic cell transformation method using P elements is based on injecting a mixture of two plasmids, one with an inserted gene coding for the transposase enzyme and one with an inserted inactive element P which bears, between the inverted repeat that recognizes the enzyme, the gene or genes to be inserted in the cell. Recently, the transposable elements Minos were identified in *Drosophila hydei* and were successfully used to transfer genes to *drosophila* and various other insects, plants and mammals. Gene transfer by Minos elements is effected by a method similar to the one described for elements P or by combining this method with one of the previously mentioned.

Transposable elements, other than vectors to insert genes into organisms, were also used to study the genome of the organisms they can be incorporated into. Each time a transposable element is inserted in a genome location, it may disturb the function of a pre-existing gene at this location and contribute to a new phenotype. Namely, transposable elements function as mutagens. Actually, as the insertion locations have

traceable characteristics, it is possible to locate the disturbed sequence of the DNA (gene). Inversely, the excision of the transposable element from the insertion position allows the disturbed gene to function again and thus eliminates the phenotype created during insertion. In this way, it can be confirmed that the disturbed gene is indeed responsible for the phenotype that was observed. So other than their mutagenic action, transposable elements are additionally used in the so-called reverse genetics.

II. Biotechnology Applications

The development of (micro)organism genetic modification techniques combined with bioinformatic tools and the data collected from the genome projects of various organisms led to an explosion of proposals for research and biotechnology applications stretching over the entire spectrum of the pharmaceutical-medical and agricultural sector. Patents are sought for all proposed applications and implementation techniques.

Patents can be divided into three categories: a) method patents, b) product patents, and, c) use patents. In the pharmaceutical industry, for example, a method patent covers the technical method for producing a pharmaceutical substance; a product patent covers the pharmaceutical substance itself; and a use patent covers a specific use of the substance. The basic difference between these three types of patents is that product patents cover every possible use of the product, even new future uses unforeseen by the claimant[7].

Product patents provide far wider coverage and it is by those that rights on DNA sequences or genetically modified organisms are granted. Use patents do not protect DNA sequences or genetically modified organisms but reduce significantly the access of third parties to the sequences or organisms. Generally, claims for patents on genes or DNA sequences take various forms that involve: entire genes, gene segments, promoters, enhancers, segments of or entire cDNA, gene mutations directly responsible for or associated with particular diseases, DNA vectors, cDNA vectors, transformed cells (by DNA vectors) or gene products (proteins). Furthermore, claims for DNA sequences are often associated with the use of proteins as drugs or the production of antibodies or methods and tools for tracing specific DNA sequences or

[7] A typical example of this aspect of product patents is the gene CCR5 which codes for a cell receptor. The HIV virus uses this receptor to penetrate cells. The CCR5 sequence first appeared in 1995 in a claim for a patent sought by the company Human Genome Sciences Inc. (HGS) under the name HDGNR10. HGS claimed that the gene (HDGNR10) coded for a cell receptor but had no idea of the part the receptor plays in the HIV/AIDS disease. The role of the gene in HIV/AIDS was first discovered in 1996 (Cell 87(3):437-46) by the team of Dr. Parmentier from the University of Pennsylvania. The Parmentier team had isolated the gene a few years earlier but they filed for a patent only after they had determined the function of the gene. The patent has not been awarded to Parmentier yet whereas HGS has already signed contracts with pharmaceutical companies to develop AIDS treatments based on the gene or on CCR5 products.

mutations. Claims for genetically modified organisms usually regard whole classes of organisms, e.g. insects or mammals containing foreign DNA sequence.

We will attempt a brief, as far as possible, presentation of a few examples of patents on DNA sequences and genetically modified organisms. The list of biotechnology applications for which patents are sought is virtually endless. Suffice it to think that in case of genes responsible for or associated with the onset of genetic disease in humans, patents were sought for diagnostic tests tracing the gene's pathogenic mutations with the obvious aim to prevent and diagnose the disease or develop gene or even cell therapies. Even the isolation and characterization of genes producing important but rare proteins has led to transgenic plants or animals with the aim to produce adequate amounts of protein using the plants or animals as bio-reactors. Genetically modified organisms (transgenic plants or animals) have been fabricated for a plethora of applications as, for example, to increase yield by inserting insect and pathogen resistant genes or to improve yield in conditions of environmental stress such as frost, drought or highly saline irrigation water or soil by integrating genes from (other) resistant (species) or to enhance their quality characteristics and nutritional value.

1. Chakrabarty's biodegrading bacteria (US 4259444)

Ananda Chakrabarty isolated four plasmids from (different) strains of the bacteria *Pseudomonas aeruginosa* and *Pseudomonas pupita*. Each plasmid bore one gene coding for the production of an enzyme that is crucial to biodegrading complex hydrocarbons. So, the CAM gene encodes the enzyme that biodegrades camphor (a linear alyphatic hydrocarbon), the OCT gene encodes the enzyme involved in biodegrading octane (cyclic alyphatic hydrocarbon), the SAL gene codes for the enzyme determining the biodegrading of salicylate (an aromatic hydrocarbon) and the NPL gene encodes the enzyme critical to breaking down naphthalene (polynuclear aromatic hydrocarbon). Chakrabarty's breakthrough was that he managed to overcome the problem of *incompatibility of plasmids inside the same bacterial cell* and to create stable strains of *Pseudomonas aeruginosa* and *Pseudomonas pupita* combining 2-4 genes from these plasmids. These new stable strains of *Pseudomonas* help to break down oil slicks more effectively. In 1972, the General Electric

Company, employer of Ananda Chakrabarty, claimed a patent for the first genetically modified microorganism.
The patent on the genetically modified bacteria of the *Pseudomonas* genus awarded at long last in 1981, at the end of a marathon of trial objections, was a landmark decision in the area of patents and, in fact, opened the way for the patenting of all genetically modified organisms.

2. Harvard's oncomouse (US 4736866, EP016972)

In the University of Harvard, the researcher Philip Leder and his post-doc Tim Stewart inserted a gene in lab mice that made them hypersensitive to breast cancer. The creation of these mice was based on the following observation: the researchers had determined that the endogenous gene myc in mice is actively involved in neoplasias when placed under the control of the appropriate promoter which is different from the promoter controlling the expression of the gene in normal circumstances. At the same time, they knew that the myc gene is homologous to the oncogene v-myc of the virus inducing neoplasia in fowl. So they attempted to create a mouse model to study neoplasias by microinjecting the gene c-myc in fertilized mice eggs under control of a different promoter than the one controlling the expression of the endogenous gene, in fact an inducible promoter. The outcome was Harvard's oncomouse that could be used either as source of cancerous cells or to test carcinogenic substances or even anti-oxidants that protect from cancer.
The claim for the patent, lodged in 1984, was not limited to the specific oncomouse that was created through the myc gene but was extended to any oncomouse that can be created with a similar method for a series of 33 different oncogenes homologous to endogenous genes in mice and humans.

3. Gene therapy for insulin dependent diabetes mellitus (EP 1223221)

Diabetes mellitus is a metabolic disease caused by insulin deficiency. Insulin dependent diabetes mellitus (IDDM) or type 1 diabetes is caused by a reduction in the secretion of insulin which results in big quantities of glucose being accumulated in blood and urine. It is an autoimmune disease, i.e. an abnormality of the immune

system involving a response against the very tissues of the same organism. The organism itself destroys the insulin-producing cells in the pancreas.
Korean researchers designed a system of two vectors for IDDM gene therapy. The first vector bears the insulin gene and the promoter of the gene K14 that is expressed in skin stem cells. The combination promoter-insulin was placed, between particular sequences recognized by the transposase enzyme of the P elements. The integration of the complex promoter-insulin in the chromosomes of epidermal stem cells is achieved by the auxiliary presence of the second vector bearing the transposase gene. Epidermal injections of the two-vector mixture in diabetic mice resulted in restoring glucose levels in blood at normal levels. In February 2001, a patent was sought for this method as well as for any method combining a similar mixture of vectors for gene therapies and also for a product containing the particular vectors to treat type 1 diabetes.

4. Manipulation of animal embryonic stem cells (EP 0695351)

One of the basic problems that face researches in maintaining or selectively propagating embryonic stem cells in lab cultures is that in reality they represent a mixture of undifferentiated (stem cells) and differentiated cells with the result that after a short period of culture they are mostly comprised of differentiated cells. This and the fact that embryonic animal stem cells were impossible to culture, even for a short period of time, if only from few lab mice strains was a basic impediment for studying stem cells in mice or in other organisms. Austin Smith's team from the University of Edinburgh found a way to distinguish between differentiated and undifferentiated cells by using the promoter of the gene Oct4 expressed in undifferentiated embryonic stem cells (blastomeres) primarily during the first stages of embryonic growth (4-8 cells). They attached the promoter of the Oct4 gene to "marker" genes in a vector and inserted the vector in embryonic stem cells. The integration of the complex "promoter Oct4 and marker-gene" into nuclear DNA leads to expression of the "marker" gene provided the cells are undifferentiated. In this way, the separation of differentiated cells (not expressing the "marker" gene) from undifferentiated cells (expressing it) is achieved. The "marker" gene may offer resistance to antibiotics and the culture of cells in the presence of the antibiotic in the medium is equivalent to automatic selection of embryonic stem cells since only the

cells resistant to the antibiotic survive, namely those embryonic stem cells expressing the “marker”.

A claim was lodged in April 1994 and issued in December 1999. The patent covered the method for isolating selecting and culturing animal embryonic stem cells, the vectors for the genetic modification (selection) of stem cells and the method for creating transgenic animals from such modified stem cells. The term “animal” stem cells, however, was not specified as usually by adding the attribute “non-human” and this gave rise to strong objections. The reason was that the modification of stem cells by the complex “promoter-marker” could extend to the genetic modification of human embryonic stem cells and the creation of transgenic humans. Objections were lodged by 14 parties among which the states of Italy, Germany and the Netherlands in March 2000. The outcome of the hearing that finally took place in July 2002 and was published on the 24th of July determines that the patent duly covered genetically modified animal or human stem cells but not embryonic stem cells.

5. Genetically modified animal tissues for xenotransplantation (WO/0188096)

One of the basic limitations in the use of animal grafts in humans consists in graft being considered as foreign body by the immune system of the host and thus being rejected. The rejection mechanism is based on the presence of antibodies in the plasma of human blood against certain animal tissue sugars. The main target of these antibodies is the oligosaccharide a-1,3gal which is added on the surface layer of animal cells with the mediation of the enzyme α-1,3gal transferase. This enzyme encodes a gene expressed in all mammals except primates (humans, chimpanzees and apes); all primates bear mutations that inactivate the gene. The company PPL Therapeutics, maker of Dolly, determined the sequence of the gene that generates the enzyme α-1,3gal transferase in sheep and designed appropriate vectors to eliminate the gene regions coding for this enzyme. The vector was used to transform somatic cells (fibroblasts) and then to place transformed fibroblast nuclei in enucleated eggs. Successive divisions of this egg led to cloned organisms that did not express one of the two copies of the gene. In case both copies of the gene are inactivated, tissues or cells from these mammals can be used as grafts in humans. The patent sought in May 2001 covered the gene sequence and its inactivation vector, the method for tracing

antibodies, the antibodies themselves, all tissues produced with this method, the method *per se* and, of course, the use of such tissues or cells as grafts in humans.
Many argue that although the expression of this gene is actively involved in graft rejection, it is not the only target of human antibodies and, consequently, this method is not going to eliminate the problems posed by xenotransplatation as the PPL Therapeutics researchers claim. All the same, the announcement in early 2002 of the birth of the first four animals bearing one inactivated copy of the gene catapulted the price of the company's shares at tremendous heights. In August 2002 it was announced that the first mice with both copies of the gene inactivated were born.

6. Familial predisposing genes to breast and ovarian cancer (EP 699754 and EP 705903)

Two genes involved in the inherited predisposition for breast cancer have been isolated to date, BRCA1 and BRCA2. The first to have been isolated was BRCA1. A variety of genetic mapping approaches were used to isolate and identify it. The first reference to the isolation of the gene dates back in 1994 from a research team of the University of Utah in collaboration with the company Myriad Genetics and the first claim for a patent was lodged in 1995. The isolation of the gene was based on work by previous researchers who identified the minimum region bearing the gene (8 cM of chromosome 17q). Next, the researchers from the University of Utah and the corporation used familiar genetic markers inside and on either side of the region to study it in extended family trees with multiple events of breast and ovarian cancer. This enabled them to reduce significantly the minimal region associated with the disease. Once this minimal region was identified, they used "scanning" methods, as they are called, in genomic banks to identify DNA sequences potentially corresponding to genes. Then they compared healthy with sick persons for DNA sequences corresponding to suspected genes until they located the sequence associated with the disease. The claim covers both the method for isolating the gene and the mutations that predispose for breast and ovarian cancer. As far as the gene mutations, in particular, are concerned, they cover approximately 34 point mutations associated with inherited predisposition for the disease. At any rate, the presence of these mutations can be used for prognosis and diagnosis purposes. The claims extend on treatment, in particular: gene therapy, protein replacement or/and protein imitation.

Myriad Genetics holds patents both from the US as well as from the European Office. The European Office granted two patents, covering BRCA1 and BRCA2 (EP 699754 and EP 705903), claimed jointly by Myriad Genetics, the University of Utah and the U.S.A. in 2001 and both were followed by objections. The first objection was filed in October 2001 and the second in February 2002. The objections were joined by interested parties from France, Belgium and Denmark, mainly spokespersons from geneticist's boards and the ministers for health of Belgium and Denmark. In both instances, the objections challenge the originality of the method and the practical applicability of the claims while accusing the claimants for insufficient description of the alleged inventions. In addition, they express strong concerns about the implications of patenting such broad claims in the area of research and public healthcare.

III. Patents for genes?

In the context of the debate on the patentability of biotechnology particular emphasis has been placed on gene patents, human or otherwise.

May genes be patented? Do they constitute discoveries or inventions? The question is meaningless for US law since discoveries are patentable there. The US Constitution (article 1, sec. 8) typically stipulates that Congress may "promote the progress of science and useful arts by securing for limited times to authors and inventors the exclusive right (of exploitation) to their respective writings and discoveries". For European law, however, the answer to this question is crucial since only inventions are patentable.

Directive 98/44/EC which has been transposed in national law recognizes the patentability not only of technical methods for isolating natural elements (genes) but also of DNA sequences or sections thereof, even if the structure of the element in question is the same as that of a natural element[8].

Yet, people have been able to recognize the existence of hereditary units (genes) and name them already from Mendel's time. The fact that they found out *how* to locate them, determine their DNA base sequence and understand their function only much later does not alter their nature as discoveries. Methods for locating, isolating and

[8] Report by the Commission to the European Parliament and the Council: Development and implications of patent law in the field of biotechnology. COM (2002) 545 final.

understanding their functions are patentable under certain conditions[9]. If this line of thinking is accepted, then genes are not patentable be they genes occurring in the natural environment (integrated in the organism's genome) or isolated from it, for instance, cloned in plasmid vectors[10]. Even if we start to understand their function and the metabolic pathways they are implicated in, these functions pre-existed and, it is argued, should not be patentable.

Notwithstanding the fact that genes are discovered and not invented, as far as the human genome, in particular, is concerned, the patentability of genes as "products" inspires concerns in view of the potential transformation of elements of the human body into marketable commodities.

Moreover, some argue that such patents have a negative impact on healthcare and research[11]. Reported examples concern mainly the patents awarded for genes *BRCA1* and *BRCA2* associated with predisposition to breast and ovarian cancer, the *APOE* gene associated with Alzheimer's disease and the gene *HFE* associated with hereditary hemochromatosis. Issuing a patent on a gene's base sequence entirely obstructs the design (by a third expert) of any genetic test for the particular sequence although it does not necessarily involve the use of a specific tracing product or tool especially designed by the patent holder. As it is, when a test is required, a license of exploitation must be purchased or the samples are sent to the patent holder's labs for analysis depending on corporate policy. This raises the test's cost and, as a consequence, limits the accessibility of patients to health care services. It has also proved to weaken the provision of medical services to patients, a fact related not only to the test's increased cost but mainly to the discovery that prefabricated tests are only able to trace a limited range of possible mutations in these genes. Thus, it is not only health care that is affected but genetic medical research is also hindered because in countries where these genes are not protected by the patents, researchers identified additional, different mutations associated with these diseases.

Another typical example of obstructing genetic research are the extremely broad patents on DNA sequences not corresponding to genes that were obtained by an Australian company 15 years ago. Now this company asks academic researchers,

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[9] See, for instance, the exception of surgical or/and diagnostic methods applied on the human or animal body.

[10] See, p.8.

[11] Lori B. Andrews (2002): Genes and patent policy. Rethinking intellectual property rights, *Nat. Rev. Genet. 3:803-808*.

from various institutions, who carry out genetic analyses based on such DNA sequences (which represent approximately 95% of the genome in higher organisms) to buy a license in order to continue their research legally[12].

Even when research is not obstructed by existing patens on genes, the very prospect of exclusive exploitation of possible findings creates barriers to research itself. A typical example is research aiming at identifying the gene associated with autism. Researchers from several university labs in the US who investigated the genetic base of the disease refused to share biological samples kept in their private collections from autistic children and their families, causing delay. By their own initiative, parents set up a non-profit making organization, Cure Autism Now (CAN), and managed to raise 5 million dollars which they used to establish a DNA bank whose material is available to any researcher wishing to investigate the genetic base of the disease.

This list is necessarily indicative and does not cover the thousands of DNA base sequences protected by patents whose impact is still unclear. According to EU data in 1996-2000 there was a spectacular increase in the number of claims for patents lodged at the European Office (EO) of the order of 226% in biotechnology and 287% in genetic engineering (the distinction was introduced by the EO) compared with the period 1986-1990. In the US, the increase recorded during the same period was even bigger. If the implications of gene patents registered to date are not the exception but the rule, then the future looks gloomy for the academic community of research at least as we knew it until now.

IV. Patents and academic research

Important changes have taken place or are underway in the field of academic research. The traditional right of exclusive exploitation of inventions by the professors-inventors themselves and not by Universities is shrinking at the European level. The exoneration of professors from the legal duty to inform their employers of their intention to claim a patent was based on freedom of science and research as embedded in constitutions even when state-funded universities. Thus, professors used to have the right to claim (or not to claim) a patent and to take all necessary steps for its industrial

[12] Geneticists question fees for use of patented "junk" DNA. *Nature 423 (8 May 2003):105.*

exploitation. Of course, patent expenses in this case were borne by professors themselves or, more often, by a third party, a partner from the industry. This legal setting is currently changing in several European countries like Germany, the United Kingdom, France and Italy[13]. Although terms and conditions in various legislations vary, in broad strokes, professors (and researchers, in general) have a legal duty to inform their employers and enjoy only part of the profits[14]. Certain academics express their concerns not only with regard to the extra red tape (the procedure for applying for research funds is now official) but mainly in respect of the free circulation of findings since they have to decide whether their work is patentable or not prior to its publication. This will have inevitable implications on the speed of diffusion of scientific knowledge, as we knew it to date[15]. Moreover, the control passes from the hands of professors-researchers inventors to the administration of Universities thus limiting their right to decide whether and to what extent they wish to exploit commercially the results of their research, if patentable.

At the same time, at the institutional level [e.g. German legislation, Developmental Policy of the European Union in the field of research and development (R&D) whereby growth is increasingly seen through the linking of the private sector to university labs], researchers and professors are enabled to set up commercial companies to exploit their inventions or to become advisers or even shareholders in biotechnology companies without conflict of interest for the researcher (at least not as a matter of law). Naturally, the evaluation of these ongoing social changes which largely imitate the American model of university market is ultimately a matter of political assessment[16].

3. THE LAW – A COMPARATIVE APPROACH

The consideration of legal issues arising from biotechnology applications starts from general patent law, on the one hand, and the familiar international instruments of bioethics, on the other hand (UNESCO's Universal Declaration on the Human

[13] Kilger C. and Bartenbach K. (2002): New rules for German professors. *Science 298 (8 Nov): 1173-5*.

[14] According to the information in the article referred to by the previous footnote, professor fees from patents are reinvested in research at least as shown by the comparative numbers of researchers employed in public or private research bodies respectively.

[15] Campaign for Cambridge Freedoms, http://cl.cam.ac.uk/~rjal4/ccf.html

[16] The 1980 Bayh-Dole Act contains similar provisions for the commercial exploitation of inventions effected with public funds.

Genome and Human Rights, the UN Convention on Biological Diversity, the Convention of the Council of Europe on Human Rights and Biomedicine). As will be seen below, patent law provisions intersect with the law of bioethics instruments.

V. Patent law

1. A general reference is the Agreement on trade-related intellectual property rights (TRIPS) by the World Trade Organization (1995). Pursuant to art. 27 of the Agreement, member-states may exclude from patentability:

- inventions whose exploitation may affect public order or morality or the protection of human, animal or plant life or health or the environment,
- diagnostic, therapeutical and surgical methods for the treatment of humans or animals,
- animals or plants (but not microorganisms),
- essentially biological processes to produce plants or animals (but not non-biological or microbiological processes).

The same article, however, stipulates that members may adopt provisions to protect *plant varieties* by "patents or by an efficient *sui generis* system or by any combination thereof".

2. In European law, the general framework as to the object of patents is set by the European Treaty on Patents (Munich 1973). Biotechnology patents, in particular, are governed by Directive 98/44/EC which has been transposed in the national law of only 6 Union members (among which Greece)[17]. Patents on microorganisms are governed by the Budapest Treaty "on the international recognition of deposit of microorganisms for the purpose of obtaining patents" (1977).

The Munich Treaty contains some interesting provisions for our topic which are identical or similar to the TRIPS provisions but *legally binding for Europe*. Thus,

[17] The three Recommendations passed by the parliamentary assembly of the Council of Europe have only a guidance value: 1240 (1994) on patents for material of human origin, 1425 (1999) on biotechnology and copyright and 1468 (2000) on biotechnology, according to which barriers against the patentability of living organisms are generally justified.

pursuant to art. 52 par. 4 the following are not considered as susceptible of industrial application:

- "methods for treatment of the human or animal body by surgery or therapy",
- "diagnostic methods practiced on the human or animal body".

Explicitly exempted from this rule are products, mainly "substances" or "compositions for use in any of these methods", i.e. basically drugs which may thus be patented.
Besides, pursuant to art. 53 patents may not be issued for:

- "inventions whose publication or application is contrary to "*ordre public*" or morality",
- "plant or animal varieties",
- "essentially biological processes for the production of plants or animals" with the exception of microbiological processes and their products.

In its interpretation of the Munich Treaty, the European Patent Office (EPO) has issued patents, among other things, for Harvard's oncomouse (1992) and for plants or parts of the human body which met with strong criticism by Non-Governmental Organizations but also by UNESCO for "over-permissive" policy. The criticisms are directed, in particular, against the blanket application of Directive 98/44/EC (see immediately below) whose legal scope extends only to those members of the Convention which are also members of the EU[18].

Added to the general provisions of the Munich Treaty are the special provisions on biotechnology laid down by the community Directive. According to the Directive:

A. The following inventions are patentable:

- inventions concerning a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used (art. 3 par. 1),
- biological material which is isolated from its natural environment or produced by means of a technical process even if it previously occurred in nature (art. 3 par. 2),

[18] For more details, see UNESCO, Intellectual Property

- inventions on plants or animals if the technical feasibility of the invention is not confined to a particular plant or animal variety (art. 4 par. 2),
- inventions that concern a microbiological or other technical process or a product obtained by means of such a process (art. 4 par. 3),
- an element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene even if the structure of that element is identical to that of a natural element (art. 5 par. 2).

B. The following inventions, however, are nonpatentable:

- plant varieties (art. 4 par. 1),
- animal breeds (art. 4 par. 1),
- essentially biological processes for the production of animals or plants (art. 4 par. 1),
- the human body at the various stages of its formation and development and the simple discovery of one of its elements, including the sequence or partial sequence of a gene (art. 5 par. 1),
- inventions whose commercial exploitation is contrary to *ordre public* or morality (art. 6 par. 1). The following are mentioned specifically:
    i. processes for cloning human beings,
    ii. processes for modifying the germ line genetic identity of human beings,
    iii. uses of human embryos for industrial or commercial purposes, and,
    iv. processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal as well as animals resulting from such processes (art. 6 par. 2).

The Directive also stipulates that the protection conferred by patents on patentable biological material or processes for the production of specific biological material also extends to any biological material derived from that biological material through

propagation or multiplication in an identical or divergent form and possessing those same characteristics (art. 8).

Besides, the protection conferred by a patent on a product containing or consisting of genetic information (provided it be patentable according to the above) extends to all material in which the product is incorporated and in which the genetic information is contained and performs its function (art 9).

At any rate, the last two provisions adopt exceptions that aim mainly at the protection of the "producer's privilege"[19].

Directive 98/44 was challenged (through an action in court by the Netherlands supported by Italy and Norway) at the European Community Court for being too "open" to biotechnology patents especially with regard to human biological material in view of the respect for human dignity. It is worth mentioning that the Council of Europe shares the views of the countries challenging the Directive[20]. The Court dismissed the action but most member-states are delaying the harmonization of their national legislation with the Directive and still view it with reproach.

Special laws – other than the Directive – in several European states tend rather to restrict biotechnology patents. The Czech legislation, for instance, is very restrictive and forbids the patenting of living organisms or elements of such organisms (cell lines, genes, DNA base sequences, etc.). The Austrian and the French legislation forbid the patenting of elements of the human organism. In contrast, elements of the human or animal or plant organisms are considered patentable by special British, Swiss or Finnish laws (in tune with the general trend discussed for Europe).

3. US law is different on two particular points on "what" may be patentable that facilitate biotechnology patents.

On the one hand, the scope of "invention" is *wider* primarily because it does not require the particular criterion of "industrial application" but the far more general criterion of "utility".

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[19] Thus, pursuant to art. 11, "the sale or other form of commercialization of plant propagating material to a farmer by the holder of the patent or with his consent for agricultural use implies authorization for the farmer to use the product of his harvests for propagation or multiplication on his own farm" whereas "the sale or any other form of commercialization of breeding stock or other animal reproductive material to a farmer by the holder of the patent or with his consent implies authorization for the farmer to use the protected livestock for an agricultural purpose. This includes making the animal or other animal reproductive material available for the purposes of pursuing his agricultural activity but not sale within the framework or for the purpose of a commercial reproduction activity".

[20] See UNESCO, Intellectual Property

On the other hand, the law *does not provide for patentability exceptions for diagnostic or treatment methods or on moral grounds*. This morally "neutral" stance of relevant legislation is confirmed by the fact that patents may be objected to only by third parties whose interests are directly injured (either before the responsible patent office or in court) whereas in European law this right pertains to anyone.

In view of all this, the US seek a review of the TRIPS Agreement to the effect of limiting the afore mentioned exceptions and making acceptable the patentability of animals and plants.

It is noteworthy that the patentability of living (transgenic) organisms in US law was recognized for the first time by the Supreme Court[21]. This precedent is still guiding the interpretation of relevant laws (35 U.S.C. 103, 1999) and the policy of the responsible Patent Office (USPTO). Thus, the USPTO excludes patents only for "natural laws, natural phenomena and abstract ideas". It also excludes "people" but not "elements isolated from the human body"[22], including organs, genes, DNA base sequences, etc.

Similarly favorable provisions toward biotechnology patents can be found, for instance, in the national legislation of Australia (only human reproduction processes are expressly excluded from patentability)[23] and Japan (allows patentability of the human organism)[24].

VI. Special bioethics law

Biotechnology patents are not governed solely by general patent law. These provisions must be construed according to a series of crucial provisions laid down by the special law on bioethics. Let us look at them at some length.

- Art. 1 of the UNESCO Universal Declaration on the Human Genome and Human Rights stipulates that the human genome is "the heritage of humanity" and art. 4 that "the human genome in its natural state shall not give rise to financial gains". At first sight, these provisions look incompatible with the patentability of genes or DNA base sequences or, in extension, with elements of the human organism containing genome sections (organs, tissues, cells).

[21] Diamond v. Chakrabarty, 1980.
[22] Patents Appeal Board (21.4.1987).
[23] Australian Patent Act , sec. 18.
[24] Patent Law, sec. 32.

- The UN Convention on Biological Diversity (Rio Convention) provides for the sovereign right of States to exploit their own natural resources (art. 3). Based on this, it lays down rules (art. 15, 16) for a fair management of these resources among States (especially commercial exploitation, access to findings of research and genetic know-how) expressly mentioning patents and intellectual property rights. The Convention is not interested in restricting biotechnology patents; on the contrary, they are taken for granted and their benefits are seen as an object of bargaining in international relationships.
- By virtue of art. 21 of the Convention on Human Rights and Biomedicine "the human body and its parts shall not as such give rise to financial gain". This principle too seems incompatible with the patentability of elements of the human body[25].

VII. Greek law

The Greek law on biotechnology patents fully agrees with the framework set by the European law instruments. Both the Munich Treaty and Directive 98/44/EC are part of Greek statutory law (Act 1607/1986 and p.d. 321/2001 respectively). Besides, the relevant provisions of the Munich Treaty are reiterated also by Act 1733/1987 which is later to the treaty's ratifying instrument[26].

Besides, as the Committee reiterated in previous reports, the above basic international instruments of bioethics are integral part of Greek legislation.

With that in mind, it would be useful to review the basic choices of our legal system along the lines of the distinction product-patents/method-patents separately for human beings, animals, plants and microorganisms.

1. Product patents

i) Human beings

[25] The wording of the EU Charter of Fundamental Rights is similar (art. 3 par. 2): "In the fields of medicine and biology, the following must be respected in particular: […] the prohibition of making the human body and its parts a source of financial gain". Anyway, the Charter is not legally binding yet.

[26] Hereinafter we will refer only to Act 1607/1986 which prevails over Act 1733/1987 because it ratifies an international treaty (art. 28 par. 1 of the Constitution).

P.d. 321/2001 explicitly excludes (art. 4 par 1)[27] the patenting of the human body at the various stages of its formation and development. If this formulation is taken strictly to the letter, it must be accepted that the "human body" exists before birth from the moment the egg is fertilized (onset of multiplication of the first cell) and during the entire period of embryonic development. This is the only way for the term "formation" (of the body), in particular, to have any meaning at all.

Patents are also excluded for all elements of the human body (organs, tissues, cells, genes, DNA base sequences) since they are simple discoveries (art. 4 par. 2). On the contrary, elements of the human body that are isolated or produced artificially even if their structure is the same as that of a natural element are patentable (art. 4 par. 2). It becomes clear from the combination of these provisions that patents are limited to artificially produced elements and may not be extended to similar natural elements prone only to discovery because this would violate the first provision.

These provisions should be considered compatible with the general clause of "morality" set forth by art. 53 Act 1607/1986 (ratifying the Munich Treaty) and, through that clause, with the afore mentioned bioethics instruments. In particular:

The interpretation of the clause can only be based on the objective element of the "moral minimum" set out unequivocally by the two bioethics instruments on the human biological idiosyncrasy, namely the UNESCO Declaration and the Biomedicine Convention. Actually, the latter is absolutely binding for the interpretation of the said p.d. since it constitutes national law (Act 2619/1998) of overriding legal effect (art. 28 par. 1 of the Constitution).

By excluding any form of commercialization of the human body or of its elements as occurring in nature[28], according to the above, these texts are in harmony with the p.d.'s prohibitions which extend to elements liable to "discovery" and distinguish between natural and artificial elements. However, can the "fabrication" of elements of human biology be "accepted" by these instruments of bioethics as patentable and, consequently, commercialized "invention"? The answer looks rather positive:

In case the "fabrication" is based on "primarily biological methods" – as would normally be expected – then the question is whether it constitutes invention, yes, but not a patentable one in the sense of articles 53b of Act 1607/1986 and 27 of the

[27] The articles mentioned belong to the p.d. and not to Directive 98/44 which is transposed by it.

[28] This seems to be the meaning of the wording "the human genome in its natural state" of the Declaration and "the human body and its parts are not as such…" of the Convention.

TRIPS Agreement. This is what these two provisions say with regard to production of plants or animals. The same should definitely – all the more so - be true of human beings (bioethics instruments explicitly prohibiting the commercialization of human beings).

It would be an exaggeration, however, to argue the same in respect of simple "elements" of human biology. The *ratio* behind the prohibition of commercialization of the human body or its elements is respect for human value. In particular, organs, tissues, cells, etc. are not "negotiable" not because of some inherent value but because they originate from or are going to be linked to a specific person. What justifies the prohibition is the risk to offend the value of this person, i.e. to transform it - even if temporarily – from a subject of law into an object, forced to sell or buy vital organs or tissues out of necessity in circumstances that degenerate his/her autonomy, and not some kind of fetishistic "sacredness" of isolated elements of the human body.

If the above are correct, then simple elements "fabricated" in the lab and not originating from nor intended for a specific person cannot be considered as connected with human value in this sense[29]. Their patentability as inventions, therefore, cannot be considered contrary to the principle of non-commercialization of the human body, as set out by the p.d.

The same arguments are obviously valid for elements fabricated by other, non primarily biological methods. These would also be patentable inventions.

ii) Animals

Pursuant to art. 53 of Act 1607/1986 the patenting of animal species is prohibited. As a matter of form, this term overrides articles 3 par. 3 and 9 par. 2 of the p.d. – which presume the patentability of animals. However, its constitutionality or compatibility with the European Convention on Human Rights (ECHR) is questionable for the following reasons:

1. The commercialization of animals is free and, in this, it comes under the protection of property and economic freedom. In this sense, it is conceivable to claim an animal patent provided it be product of "invention". It is worth

[29] They may prove valuable at some future moment but not more so than would have been the case with water in the desert or with food in times of famine: neither water nor food have ever been exempted from trade for this reason.

stressing at this point that art. 53 of Act 1607/1986 does not question whether an animal can be product of "invention": it simply forbids the patentability of such invention.

2. The "invention" of a new animal – usually by manipulating the genome of a known animal – should not be considered *a priori* as contrary to the constitutional principle of protection of the natural environment (in the sense that it constitutes a violent intervention in the evolution of the species potentially threatening biodiversity in the long run) or the constitutional right to healthcare (in the sense that it may cause disease or epidemics). An absolute reservation on all animal species (even lab insects) without a concrete assessment of the potential risks (the interpretation adopted for "the precautionary principle"[30] by the Convention on Biological Diversity) would overlook the ability – not limitless but existing nevertheless – of science to make forecasts about environmental impact and is on the verge of encroaching upon the core of freedom of research.
3. On the other hand, any injury to the animal's condition, especially from the suffering or pain inflicted to it, would be in direct violation of another aspect of the constitutional protection of the environment and the *ad hoc* legislation on animal protection (which has overriding legal effect). This scenario, however, is already avoided explicitly by art. 4 par. 2 (d) of the p.d. which prohibits patents for animals produced by genetic intervention which is painful to them or to the animals they originated from.

Elements of animal bodies are patentable provided they be "created" artificially to the extent that the reservations discussed for human beings do not apply here.

iii) Plants

Again, art. 53 of Act 1607/1986 prohibits the patenting of plant varieties or plants created with primarily biological processes. This provision prevails over articles 3

[30] The "precautionary principle" according to which when there is a threat of serious or irreversible damage to the environment or human health, scientific uncertainty cannot be the reason for putting off measures to prevent the damage, is a fundamental principle of environmental law. See, e.g., G. Balia, "Carthage Protocol on the prevention of biotechnological risks. A change of paradigm in international environmental law", http://www.nomosphysis.org.gr (Articles, March 2000).

par. 3 and 9 par. 1 of the p.d. However, the above comments are also true with respect to plants. Thus, in this case as well, the compatibility of art. 53 with the Constitution or the ECHR is doubtful. In particular:

1. As with animals, the commercialization of plants is free. Therefore, their patenting as an aspect of economic freedom cannot be excluded in principle provided a given variety be product of "invention" (an accepted assumption in art. 53, as with animals).
2. Likewise, the invention of new plant varieties cannot be considered *a priori* as injurious to the environment or the right to healthcare. The "precautionary principle" calls for the assessment of potential risks and not for an *a priori* absolute barrier on freedom of research.

iv) Microorganisms

The patentability of genetically modified microorganisms as products of "invention" is explicitly acknowledged by art. 53 par. b (b') of Act 1607/1986 and by Act 2128/1993 ratifying the special "Budapest Convention" on the patentability of microorganisms[31].

2. Method patents

Pursuant to art. 3 par. 1 of the p.d. 321/2001 the patenting of methods "for the production, processing or use of biological material" is allowed in principle. On the other hand, art. 5 par. 1 excludes the patenting of inventions whose "industrial exploitation is counter to public order or morality". Starting from these general principles it may be said that:

i) Human beings

1. By virtue of art. 52 of Act 1607/1986 the following are not considered "inventions susceptible of industrial application" and are therefore unpatentable:

[31] P.d. 321/2001 did not transpose the respective provision of art. 4 of Directive 98/44/EC. In view of the above legislation on microorganisms and the interpretation of the original text of the Directive, the patentability of microorganisms is not put in question.

a) methods of surgical or therapeutic treatment, and,

b) diagnostic methods on the human body.

However, the law accommodates patents for products, mainly "substances or compositions" used in the application of one of these methods. At any rate, this does not deny the fact that the patentability of these – eventually biotechnological – methods is excluded.

2. P.d. 321/2001 does not specify which biotechnological methods related to human beings are patentable. It relies on the above general principles effective for all natural species. It does specify the opposite, namely which methods are unpatentable:

a) methods for cloning human beings,

b) methods for modifying the human germ line genetic identity, and,

c) the use of human embryos for industrial or commercial purposes.

These are just examples of methods whose commercial exploitation is counter to "public order or morality" (art. 5). So, apart from these specific examples, there is a wide margin of interpretation to identify nonpatentable methods related to human beings or counter to public order or morality. Noticeably, the wording of p.d. 321/2001 is similar to that of art. 53 of Act 1607/1986[32] and to the TRIPS Agreement which reflects a common position in patent law.

The criteria to be used in order to identify other instances counter to public order or morality include, of course, overriding rules of law related to human rights and primarily the Constitution, the ECHR, the Convention on Human Rights and Biomedicine, other international instruments of overriding legal effect in our legal system but also non binding documents such the Universal Declarations by the UN on Human Rights and by UNESCO on the Human Genome and Human Rights.

These documents indicate that the general rule of respect for human value – which absolutely forbids that a person be transformed into a "means" for research or for any other purpose and is individuated into specific criteria such as free and informed consent or protection of privacy or personal data – is the yardstick for any interpretation of these vague concepts. At any rate, what this principle seems to require of the patent office is to verify as a precaution and *in concreto* whether these criteria are met. The principles of respect for human value and human rights have implications for the overall legal assessment of any method including the evaluation

[32] The terms "publication or application" are used instead of "commercial exploitation".

of a patent claim – and not only of the final stage of "commercial exploitation" or "publication" or "application" – since they emanate from prevailing provisions of law. Of course, it is not unthinkable that the commercial exploitation of a totally acceptable method prove to be counter to morality or public order. But the method itself may also infringe these clauses (because it requires an illegitimate use of personal data, for instance). The patenting of such methods on humans could not be accepted even with the provision that they not be used commercially.

ii) Animals

1. As with human beings, the following are not considered "inventions susceptible of industrial application" by virtue of art. 52 of Act 1607/1986 and are, therefore, nonpatentable:
a) methods of surgical or therapeutic treatment, and,
b) diagnostic methods on animal bodies.
2. Art. 53 of the said Act excludes the patentability of "primarily biological methods" to produce animals. The definition of this notion is found in art. 2 of the p.d. 321/2001: "A process for the production of plants or animals is primarily biological if it consists entirely of natural phenomena such as cross-breeding or selection".
3. As for the rest, the afore mentioned principles embedded in p.d. 321/2001 apply also in animals. Any methods counter to public order or morality are explicitly excluded from patentability. By way of indication, art. 5 mentions as an example methods for modifying the germ line genetic identity of animals that may cause suffering without substantial medical benefit for man or animal".
Here too the individuation of the vague concepts "public order" and "morality" in order to determine these methods more accurately or to identify others will be based on art. 24 par.1 of the Constitution on the protection of the "natural environment" (from which the principles of respect of biodiversity and of natural species in general emanate) and on overriding laws on animal and environmental protection. In particular, the following legislation applies:

- Act 2015/1992 on the protection of vertebrate experimental animals (European Treaty – overriding legal effect),
- Act 1197/1981 "on the Protection of Animals",

- Act 2204/1994 on biological diversity (Rio Convention – overriding legal effect) to the extent it lays down terms for the preservation of biodiversity on grounds other than protection of animals *per se* (e.g. protection of human health or equilibrium of ecosystems)[33]. Thus, a method related to animals can be contrary to public order or morality not because it is harmful for the animal itself but because its implementation may disturb the ecosystem in general.

iii) Plants

1. Art. 53 of the Act 1607/1986 prohibits the patenting of "primarily biological methods" for the production of plants as discussed above with regard to production of animals.
2. The general principles enshrined in p.d. 321/2001 are also applicable here. The opposition of a method related to plants to public order or morality excludes patenting pursuant to art. 5 of the p.d. and art. 53 of the Act 1607/1986. There is no indicative listing of such methods for plants. The criteria to identify such methods must be sought in provisions for the protection of the natural environment or biodiversity (art. 24 par. 1 of the Constitution, Act 2204/1994). The opposition to public order or morality here has to do with the protection of healthcare and certified risks rather than with the reversal of ecological balance.

iv) Microorganisms

Microbiological methods are patentable by virtue of art. 53 of the Act 1607/1986, Directive 98/44/EC (art. 4 par. 3)[34] and also the Budapest Convention (Act 2128/1993). Again, exceptions to the patentability of methods related to microorganisms can be justified if they are counter to public order or morality for reasons mainly pertaining to protection of healthcare or the environment. The criteria – neither exclusive nor legally binding – to evaluate these methods can be found in the detailed provisions of Directive 90/219/EEC as amended[35] which specify security

[33] See, for example, art. 8 (g) on "biotechnologically modified living organisms".
[34] Cf. footnote 13.
[35] Based on a Joint Ministerial Decision no 95267/1893/1995 (Official Gazette/ B' /1030).

parameters for the use of genetically modified microorganisms[36] and in the respective articles of amending Directive 98/81/EC[37].

4. THE FRAMEWORK FOR BIOETHICS

Biotechnology patents are governed by explicit legislative choices or by choices read "between the lines" of various provisions. This chapter examines whether the legal choices described above are justified from the ethical/social viewpoint.
For this purpose, it is necessary, first of all, to come back to the definition of "patent": for a product of the mind to be patented, it must be *novel*, involve *inventive activity* and be susceptible of *industrial application*. After this preliminary check, it must be examined whether, even when all the elements of "invention" are present, a patent would nevertheless not be justified in ethical/moral terms – based on other grounds.

A Conceptual elements of patent

I. The criterion of "inventive activity" is not met: The discovery of an element occurring naturally cannot be patented even if the method leading to the discovery is scientifically novel (cf. point II below).

The reason patents protect "inventions" but not "discoveries" is that they are intended as rewards for inventiveness (scientific or technical novelty) in itself and not as means to secure "market shares". If the latter were the case, "discoveries" would simply be patentable. The commercial utilization of a patented invention is only a derivative, an eventuality, independent in principle from the patent itself. Therefore, the crucial element is to document "inventiveness".
The discovery of an element occurring naturally does not involve "inventiveness" since it is not the cause of existence of this element. Therefore, the eventual "inventiveness" of the method used to isolate this element cannot reasonably be considered as "incorporated" in the latter.

[36] See Annex III in particular.
[37] See Annexes III and IV in particular. The Directive has not been transposed in our national law yet.

Thus, if the purpose of patent is to reward inventiveness, it is necessary to distinguish as clearly as possible between elements occurring naturally – and therefore prone to "discovery" only – and elements occurring in nature for the first time as biotechnology applications; the latter are patentable. It becomes obvious then that the isolation of DNA sequences (e.g. genes, promoters, enhancers, etc.) from various organisms constitutes a discovery whereas the creation of DNA vectors combining DNA sequences in a way that does not exist in nature may be considered as invention. In the same vein, any unrecorded yet species of organisms will be discoveries when they will be found out whereas transgenic organisms may be considered as inventions since they correspond to genetic combinations that could not have arisen out of natural processes.

Although the genes of a natural organism are unpatentable, the *use* of the gene's DNA sequence may be patentable provided the elements of inventiveness and industrial application are present. Diagnostic tests developed to trace mutations associated with or inducing genetic diseases should come under the category of *use* patents[38]. However, claims for the *use* of the diagnostic test should cover *only* the specific diagnostic test and not *any* diagnostic test that may be based on the information potential of the genes associated with or responsible for the particular disease.

In this respect, the provisions of Directive 98/44/EC and p.d. 321/2001 that allow the patentability of biological material which pre-exists in nature are not justified. In contrast, the prohibition of patenting plant varieties, animal species and essentially biological methods to produce animals or plants is justified (because they are equivalent to natural laws).

II. <u>The criterion of "inventive activity" is met:</u> The fabrication of a biological combination of elements or of a new organism is patentable, if said combination or organism does not occur naturally. The method used to isolate an element occurring naturally is patentable in itself.

Provided they do not infringe the value of human beings or the closely related values of protection of the natural environment and healthcare, there does not seem to be any

[38] As a matter of fact, this is not permitted by the law in force (art. 52 par. 4 Act 1607/1986) because it regards "diagnostic methods". However, this begs the question of such methods not being developed because related research is economically unattractive without the prospect of patent.

other “principle” excluding that inventiveness be rewarded by patents for biological inventions.
Whenever it is certain that a combination of elements (for instance, a DNA sequence or a new organism) does not occur naturally, “inventive activity” should be accepted as with any novel combination of inorganic natural elements.
The same should be valid for novel scientific or technical biotechnological methods aiming at fabricating products that do not occur naturally or at isolating existing elements: although the latter are non patentable, as discussed above, the methods *per se* do constitute “inventions” and are patentable.

In the light of this general context, the general provision of art. 3 par.1 of Directive 98/44/EC makes sense.

III. *The criterion of “industrial application” is met: The object of patent must be specific and stable*.

If the object of patent is not specific and stable, namely if it is not individuated based on its particular characteristics, certainty in trade would be at stake and so would legal certainty because there would be a risk of overlapping rights pertaining to several rightholders.
How “specific” should the object of patent be? For instance, in the example of Harvard’s oncomouse, the claimants sought a patent on all oncomice created by inserting in the mouse genome any of the 33 oncogenes listed in their claim. The claimants themselves, however, presented only one specific application, so their claim was based on the *assumption* that all the oncogenes in their list would behave in a *likewise* (*but not necessarily identical*) way when and if inserted in the mouse genome. Of course, one could reasonably retort that to limit the scope of patent not only fails to reward the claimant’s inventiveness but does not produce the necessary economic stimulus to invest in biotechnology. Still it would be more rational for researchers (applicants and competitors) and investors alike to ground their claims on evidence rather than on assumptions. Moreover, instead of extending the patent to the entire vegetal kingdom, for example, claims (for product, use or method patents) should preferrably be limited to those taxonomic categories (e.g. species, families) in respect of which evidence is produced to document at least a *mutatis mutandis*

application. This criterion seems able to overcome the problem of overlapping claims between different applications while at the same time promoting the development of research to the benefit of public interest.

B. Unpatentable "inventions"

Although they do constitute "inventions", certain products of the mind are absolutely non-patentable because they infringe upon the value of human beings as overriding principle of modern civilization or upon goods directly related with this value such as the natural environment and healthcare, in particular.

This position is justified because, as with any individual fundamental right, the right to property and economic freedom underlying the institution of patents *presupposes* respect for the value of human beings: the latter is the source of all individual expressions of our autonomy – which are derivatives.

Human value, however, even though conceived "in the abstract" – independently from natural, historical, geographical, cultural or other attributes – does not have a mere "nominal" value. Since persons are not transcendental beings but have a biological presence as any other living organism, its enjoyment in practice necessarily depends on a vital "material substratum" having the natural environment and human health at its core. In this respect, these two goods are to be considered as additional conditions to enjoy any individual right including the right to property or economic freedom.

Therefore, when human value or the natural environment or health are immediately at stake there can be no scope for patentability: *these goods are not weighed against but absolutely prevail over the protection of property or any other right*.

Thus, the law *forbidding the patentability of the human body* is justified in moral/social terms, if human beings are meant as holistic creatures. For even if it were possible to fabricate a person, issuing a patent for him/her would inescapably offend his/her human value; it would involve a form of totally imposed determinism, of transforming him/her from a subject of social coexistence into an "object".

In the context of respect for the natural environment or for health, the same can be argued with regard to the creation of *new* plant varieties, animal species or microorganisms or even individual plants or animals or, generally, any novel

intervention in an organism's genome if this *disrupts the balance of ecosystems* and threatens environmental disasters or if the release of such organisms in the environment or through the food chain involves a documented risk to *induce disease*, etc.

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