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Industrijsko vlasništvo i biotehnologija

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Summary

The modern concept of industrial property includes the following subjects: patent, utility model, industrial design and trade mark. Of special interest are the rights in biotechnology, where patent protection is specifically regulated. The roots of the present European Patent System draw back to 1953, when the first negotiations concerning a common European Patent System have been started. As the first result of these discussions, the so-called Strassbourg Convention was signed in 1963, in which Article 2(b) is concerned with the area of biotechnology. The industrial property rights in biotechnology are constantly harmonized by WIPO (World Intellectual Property Organization). In the International Patent Classification (IPC) the area of biotechnology is covered by the subclasses C12N through C12Q. Each non-living matter obtained by biotechnological processes can be patented. Microorganisms can be protected by patents too, but the deposit of the invented microorganism is obligatory at an official depository institution. The jurisdiction of the European Patent Organization (EPO) generally excludes plant and animal varieties from patent protection. The number of patents in the area of genetic engineering is growing faster than the total field of biotechnology, so that its portion of about 25 % at the beginning of the eighties has reached about 40 % in 1989, with an absolute number of 1000 patents.

Sažetak

Današnja koncepcija industrijskog vlasništva obuhvaća patent, industrijski uzorak, te trgovački i uslužni pečat. Područje posebnog interesa industrijskog vlasništva čine prava u biotehnologiji, gdje je patentna zaštita posebno regulirana. Godine 1953. započeli su pregovori o europskom patentnom sustavu, a prvi rezultat tih rasprava bila je konvencija Strassbourg potpisana 1963. godine, u kojoj se članak 2(b) odnosi na područje biotehnologije. Prava industrijskog vlasništva u biotehnologiji usklađuje WIPO (World Intellectual Property Organization). U internacionalnoj patentnoj klasifikaciji (IPC, International Patent Classification) područje biotehnologije obuhvaćeno je podskupinama od C12N do C12Q. Patentirati se može svaka neživa tvar dobivena biotehnološkim procesom. Također se mogu patentirati i mikroorganizmi, ali se njihova pohrana mora provesti u skladu s budimpeštanskim ugovorom (1980. god.) o internacionalnoj pravovaljanosti pohrane unutar patentne prijave. Europska patentna organizacija (EPO) isključuje mogućnost patentne zaštite biljnih i životinjskih vrsta. Broj patenata iz područja genetičkog inženjerstva povećava se brže nego ukupni broj patenata iz svih područja biotehnologije. Početkom osamdesetih godina patenti iz genetičkog inženjerstva iznosili su 25 % da bi 1989. godine, s 1000 patenata, porasli na 40 % od ukupnog broja svih patenata s područja biotehnologije.

Some of the most important consequences of the progress in industrial products and processes are related to industrial property protection. The process of patent protection began with the Paris Convention in 1830 and the Berlin Convention in 1866, where the basic principles of industrial property protection were laid down. The roots of the present European Patent System, as opposed to the national patent offices, draw back to the fifties, when the first negotiations about a common European patent system began. The first result of the negotiations was the Strassbourg Conventoin, signed in 1963, which represents the basis of the existing European Patent System. At the European Patent Conference in Munich (1973) the organization of the European Patent Office (EPO) was proposed, with the aim to create an European system for granting patents. The EPO was organized and became active in 1978.

In order to be protected by a patent, an invention, according to the majority of national legislations, should comply with some requirements as to concepts of: nov-

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elty, inventive step, industrial applicability and sufficiency of description of the invention. In other words, an invention is new if it was not known or available to others prior to the date of application of the invention. Thus, the purpose of the patent system is to promote technology through new inventions and to prevent inventions from remaining secret *(1)*.

Inventions in engineering and those branches of the natural sciences that deal with inanimate matter are easily patentable. In the case of living matters, certain problems arise. Most patent laws make a distinction between discovery and invention and exclude mere discovery from the benefit of patent protection. Everything that pre-exists in nature, without human interference, as well as the phenomena and intrinsic properties referred to natural products or natural laws, may be considered as discovery.

In the field of biotechnology, the occurrence of a number of substances, microorganisms and other material raises an immediate question concerning the protection of possible discovery and the question under which conditions it may be treated when considering the concept of novelty. The European Patent Office (EPO) in its official Guidelines promotes the view that an invention should not be considered unpatentable for the reason only that it is composed of living matter, and their statement is as follows:

»To find a substance freely occurring in nature is also mere discovery and therefore, unpatentable. However, if a substance found in nature has first to be isolated from its surroundings and a process for obtaining it is developed, that process is patentable. Moreover, if the substance can be properly characterized either by its structure, by the process by which it is obtained or by other parameters, and it is 'new' in the absolute sense of having no previously recognized existence, then the substance per se may be patentable. An example of such a case is that of a new substance which is discovered as being produced by a microorganism.«

The position of EPO on this issue is shared by the most industrially developed countries of Western Europe and is endorsed by the European Commission *(2)*.

An universal requirement of international patent law is that every patent provides a disclosure sufficient to enable a skilled person to perform the process or make the product for which the patent has been granted. One of the most discussed aspects concerning patentability of biotechnological inventions is the sufficiency of disclosure and the possibility to repeat the invention. It is necessary that a patent application be sufficiently understandable and supply all necessary information so as to make possible its reproduction and use.

Considering that biotechnology deals with microorganisms and other living matters, and that they have extremely complex structures, it is very difficult to describe them in an appropriate way. This problem was overcome by the use of culture collections as patent depositories for microorganisms and other incompletely describable biological materials. The details for this procedure are fixed in Rules 28 and 28a of the European Patent Convention. This practice is now adopted by all member states of the EPC. Deposit of microorganisms therefore, supplements the written disclosure by providing a source of biological material from which third parties can obtain samples in order to perform what is described in the patent application *(2)*.

For the purpose of international patenting procedure the Budapest Treaty simplifies the requirement of microorganism deposits, when the same invention needs protection in several countries simultaneously. It establishes that the microorganism deposited in one contracting state is recognized as such by other member states. The deposit shall be effected at the filing date of the patent application and the sample storage lasts 30 years.

The deposition provides a legal solution for sufficiency of patent disclosure, but does not necessarily provide a commercially acceptable solution. For all other types of invention the inventor provides only information, whereas in biotechnology he must provide the microorganism through which the benefits of the invention are realized. The organism itself provides much of the know-how, therefore, the access to such biological material is of the greatest commercial importance. In losing control of the deposited microorganism at the application date, the applicant is at the point of maximum weakness. Accepting that the original deposit requirements were problematical EPO has introduced »independent expert solution«. The sample is released to the expert who can do all that is required by the party on whose behalf he acts, except that he cannot pass the sample to such party *(3)*.

At present, each non-living matter obtained by technological processes, as well as biotechnological processes, especially genetic engineering, can be protected by patents, but genetic material in the form in which it is present in nature cannot be patented. However, it is possible that after identification and isolaiton in an usable form for transference to other plants or other living material, such genetic material could be the subject of a patent. Therefore, living matter, including microorganisms which are the product of a biotechnological process can be patented.

According to EPC, patents shall not be granted in respect of »plant or animal varieties or essentially biological processes for the production of plants and animals«.

As to animal varieties, they are excluded from patentability, whereas animals as such can be patented. The expression variety in the context of animals denotes only morphological or phenotype divergences. According to this opinion, animal species should be excluded from patentability, because they are groups of animal populations and not well defined individuals. The transgenic animal like the so-called onco-mouse of the Harvard University is patentable, because the onco-mouse is no animal variety.

In order to get an overview of patents in biotechnology, the use of International Patent Classification is helpful, where the area of biotechnology is defined by the so-called sub-classes C12M through C12Q. The contents of these subclasses are presented in Table 1 *(4)*.

The main group C12N15 of the International Patent Classification concerning genetic engineering, is presented in Table 2 *(4)*. Therein application-oriented items

Table 1. Definition of biotechnology by subclasses of the International Patent Classification (IPC) *(4)*
Tablica 1. Definicija biotehnologije prema podrazredima međunarodne patentne klasifikacije (IPC) *(4)*

C12M	Apparatus for enzymology and microbiology *This group covers:*
1/00	– apparatus where microorganisms or enzymes are produced or isolated – apparatus where the characteristics of microorganisms or enzymes are investigated – apparatus specifically adapted to employ microorganisms or enzymes as »reactants« or biocatalysts
3/00	– tissue, human, animal or plant cell, or virus culture apparatus
C12N	Microorganisms or enzymes; composition thereof
1/00	– processes of propagating, maintaining or preserving microorganisms or compositions thereof
3/00	– spore-forming or isolating processes
5/00	– undifferentiated human, animal or plant cells, tissues; cultivation or maintenance thereof – plant reproduction by tissue culture techniques
7/00	– viruses; composition, preparation and purification thereof
9/00	– enzymes, proenzymes; composition thereof
11/00	– carrier-bound or immobilized enzymes, carried-bound or immobilized microbial cells; preparation thereof
13/00	– treatment of microorganisms or enzymes with electrical or wave energy, e.g. magnetism, sonic waves
15/00	– mutation or genetic engineering
C12P	Fermentation or enzyme-using processes to synthetize a desired chemical compound or composition or to separate optical isomers from a racemic mixture
1/00	– preparation of compounds or compositions by using microorganisms or enzymes
3/00	– preparation of elements or inorganic compounds except CO_2
5/00 to 15/00	– preparation of acyclic or carbocyclic organic compounds
17/00	– preparation of heterocyclic carbon compounds
19/00	– preparation of compounds containing saccharide radicals
21/00	– preparation of peptides or proteins (single cell proteins, monoclonal antibodies)
23/00	– preparation of carotenes
25/00	– preparation of riboflavins
27/00	– preparation of gibberellin
29/00	– preparation of tetracycline
31/00	– preparation of prostaglandins
33/00	– preparation of steroids
35/00	– preparation of cephalosporin
37/00	– preparation of penicillin
39/00	– other processes for biosynthesis preparations
41/00	– separation of optical isomers
C12Q	*Measuring or testing processes involving enzymes or microorganisms (immunoassay); compositions or test papers thereof; processes of preparing such compositions; condition-responsive control in microbiological or enzymological processes*
1/00	– measuring or testing processes involving enzymes or microorganisms; processes of preparing such compositions
3/00	– condition-responsive control processes

like the production of e.g. interferons, interleukins, hormones are followed by the more basic oriented parts like the use of vectors for introducing foreign genetic material into prokaryotes or eukaryotes as hosts.

It is interesting to follow the biotechnology's potential for becoming a driving economic force, although it is evident that putting the new scientific knowledge to industrial use is a considerable task. The number of patents at the EPO in the area of biotechnology is constantly growing. The total number of European patent applications, including all sectors nearly doubled from 1980 till 1987, but the increase in biotechnology patent application was threefold. Great rise was noticed in the fields of genetic engineering and genetic enzymology (number of applications in 1986 was 4.75 times higher than in 1980). Nearly the same increase was noticed in patent applications of biosynthetic compounds *(5)*. Nevertheless, there is a general upward trend of research and development in biotechnology. According to Fig. 1, genetic en-

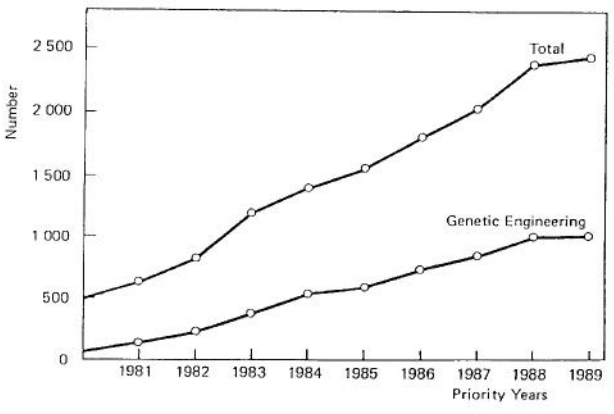

Fig. 1. Number of patents at the EPO in the area of biotechnology *(6)*
Slika 1. Broj patenata u EPO (europski patentni ured) iz područja biotehnologije *(6)*

Table 2. Main group C12N15 of the International Patent Classification concerning genetic engineering *(4)*
Tablica 2. Glavna skupina C12N15 međunarodne patentne klasifikacije koja se odnosi na genetičko inženjerstvo *(4)*

15/00 Mutation or genetic engineering; DNA or RNA concerning genetic engineering, vectors, e.g. plasmids, or their isolation, preparation or purification; Use of hosts therefor

Note
This group covers processes wherein there is a modification of the genetic material which would not normally occur in nature without intervention of man which produce a change in the gene structure which is passed on to succeeding generations.

15/01 Preparation of mutants without inserting foreign genetic material therein; Screening processes therefor
15/02 Preparation of hybrid cells by fusion of two or more cells, e.g. protoplast fusion
15/03 Bacteria
15/04 Fungi
15/05 Plant cells
15/06 Animal cells
15/07 Human cells
15/08 Cells resulting from interspecies fusion
15/09 Recombinant DNA-technology
15/10 Processes for the isolation, preparation or purification of DNA or RNA (chemical preparation of DNA or RNA C 07 H 21/00; preparation of non-structural polynucleotides from microorganisms or with enzymes C 12 P 19/34)
15/11 DNA or RNA fragments; Modified forms thereof (DNA or RNA not used in recombinant technology C 07 H 21/00)
15/12 Genes encoding animal proteins
15/13 Immunoglobulins
15/14 Human serum albumins
15/15 Protease inhibitors, e.g. antithrombin, antitrypsin, hirudin
15/16 Hormones
15/17 Insulins
15/18 Growth hormones
15/19 Interferons; Lymphokines; Cytokines
15/20 Interferons
15/21 Alpha-interferons
15/22 Beta-interferons
15/23 Gamma-interferons
15/24 Interleukins
15/25 Interleukin-1
15/26 Interleukin-2
15/27 Colony stimulating factors
15/28 Tumor necrosis factors
15/29 Genes encoding plant proteins, e.g. thaumatin
15/30 Genes encoding protozoal proteins, e.g. from Plasmodium, Trypanosoma, Eimeria
15/31 Genes encoding microbial proteins, e.g. enterotoxins
15/32 Bacillus crystal proteins
15/33 Genes encoding viral proteins
15/34 Proteins from DNA viruses
15/35 Parvoviridae, e.g. feline panleukopenia virus, human parvovirus
15/36 Hepadnaviridae
15/37 Papovaviridae, e.g. papillomaviruses, polyomavirus, SV40
15/38 Herpetoviridae, e.g. herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, pseudorabies virus
15/39 Poxviridae, e.g. vaccinia virus, variola virus
15/40 Proteins from RNA viruses, e.g. flaviviruses
15/41 Picornaviridae, e.g. rhinovirus, coxsackie viruses, echoviruses, enteroviruses
15/42 Foot-and-mouth disease virus
15/43 Poliovirus
15/44 Orthomyxoviridae, e.g. influenza virus
15/45 Paramyxoviridae, e.g. measles virus, mumps virus, Newcastle disease virus, canine distemper virus, rinderpest virus, respiratory syncytial viruses
15/46 Reoviridae, e.g. rotavirus, bluetongue virus, Colorado tick fever virus
15/47 Rhabdoviridae, e.g. rabies viruses, vesicular stomatitis virus
15/48 Retroviridae, e.g. bovine leukaemia virus, feline leukaemia virus, HIV
15/49 Lentiviridae, e.g. immunodeficiency viruses, visna-maedi virus, equine infectious anaemia virus
15/50 Coronaviridae, e.g. infectious bronchitis virus, transmissible gastroenteritis virus
15/51 Hepatitis viruses
15/52 Genes encoding for enzymes or proenzymes

Note
In this group:
– genes encoding for proenzymes are classified with the corresponding genes encoding enzymes;
– enzymes are generally categorised according to the »Nomenclature and Classification of Enzymes« of the International Commission on Enzymes. Where appropriate, this designation appears in the groups below in parenthesis.

15/53 Oxidoreductases
15/54 Transferases
15/55 Hydrolases
15/56 acting on glycosyl compounds, e.g. amylase, galactosidase, lysozyme
15/57 acting on peptide bonds
15/58 Plasminogen activators, e.g. urokinase, TPA
15/59 Chymosin
15/50 Lyases
15/61 Isomerases
15/62 DNA sequences coding for fusion proteins

Note
In this group, the following term is used with the meaning indicated:
– »fusion« means the fusion of two different proteins.

15/63 Introduction of foreign genetic material using vectors; Vectors; Use of hosts therefor; Regulation of expression
15/64 General methods for preparing the vector, for introducing it into the cell or for selecting the vector-containing host
15/65 using markers (enzymes used as markers 15/52)
15/66 General methods for inserting a gene into a vector to form a recombinant vector using cleavage and ligation; Use of non-functional linkers or adaptors, e.g. linkers containing the sequence for a restriction endonuclease

Note
In this group, the following expression is used with the meaning indicated:
– »non-functional linkers« means DNA sequences which are used to link DNA sequences and which have no known function of structural gene or regulating function.

15/67 General methods for enhancing the expression
15/68 Stabilisation of the vector
15/69 Increasing the copy number of the vector
15/70 Vectors or expression systems specially adapted for *E. coli*

Notes
(1) This group covers the use of E. coli as host
(2) Shuttle vectors also replicating in E. coli are classified according to the other host.

15/71	Expression systems using regulatory sequences derived from the trp-operon
15/72	Expression systems using regulatory sequences derived from the lac-operon
15/73	Expression systems using phage lambda regulatory sequences
15/74	Vectors or expressions systems specially adapted for prokaryotic hosts other than *E. coli*, e.g. Lactobacillus, Micromonospora

Note
This group covers the use of prokaryotes as hosts.

15/75	for Bacillus
15/76	for Actinomyces; for Streptomyces
15/77	for Corynebacterium; for Brevibacterium
15/78	for Pseudomonas
15/79	Vectors or expression system specially adapted for eukaryotic hosts;

Note
This group covers the use of eukaryotes as hosts.

15/80	for fungi
15/81	for yeasts
15/82	for plant cells
15/83	Viral vectors, e.g. cauliflower mosaic virus
15/84	Ti-plasmids
15/85	for animal cells
15/86	Viral vectors, e.g. vaccinia virus
15/87	Introduction of foreign genetic material using processes not otherwise provided for e.g. co-transformation
15/88	using micro-encapsulation, e.g. using liposome vesicle
15/89	using micro-injection
15/90	Stable introduction of foreign DNA into chromosome

gineering is growing faster than the total field of biotechnology, so that its portion of about 25 % at the beginning of the eighties has reached about 40 % in 1989, with an absolute number of 1000 patents. These data indicate that there are no special problems of patenting inventions in the area of genetic engineering *(6)*.

Looking at the countries of origin, the United States are dominating with a slightly growing tendency and have reached an overall share of nearly 50 % (Fig. 2). Between the observation periods of 1984 – 1986 and 1987 – 1989 there is a growth in Japan, Germany, France and United Kingdom, but less distinct than for the United States. The general structure of Fig. 2 is valid for most of the subfields of biotechnology. A stagnation of the number of patents of Europan origin can be observed in the period 1987–1989. These signs of stagnation seem to reflect the experiences of many companies that the research and development process for getting marketable results is often more time-consuming and more expensive than assumed beforehand *(6)*.

The number of patents for the application areas of pharmaceutics, agriculture and food, in the period 1981 – 1989, are presented in Fig. 3, wherein pharmaceutics is, of course, the largest topic. The high number of about 900 patents in this area is a proof for a quite high activity. According to Fig. 3, the application areas of agriculture and food are much smaller than that of pharmaceutics. The agro-related biotechnology started at a very low level in the beginning of the eighties, but grew steadily, so that there are now higher patent numbers than in the food area. Within this area the subfields of biocides and plant breeding are the most important ones, whereas animal breeding remains at a quite low level *(6)*.

Observation about biotechnology in the Republic of Croatia

Development of biotechnology in the Republic of Croatia begins with the foundation of the Biotechnological Faculty in Zagreb, at the end of the fifties and the erection of the biotechnological department at the Pliva factory in 1960. The production of the antibiotic oxytetracycline at the Pliva factory gave an impetus to the advancement of biotechnology in Croatia. Despite the scientific results at

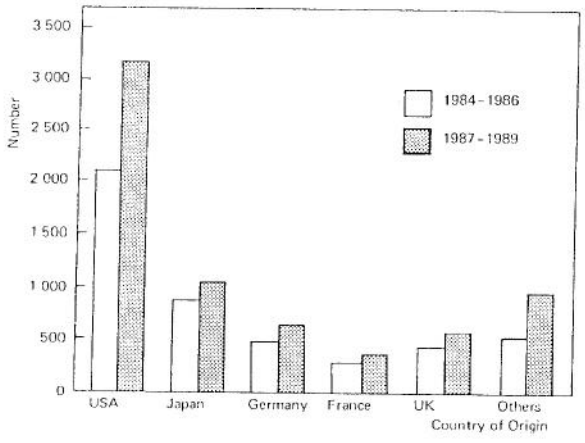

Fig. 2. Biotechnology patents at the EPO according to countries of origin *(6)*
Slika 2. Patenti iz biotehnologije u EPO, razvrstani prema zemljama iz kojih potječu *(6)*

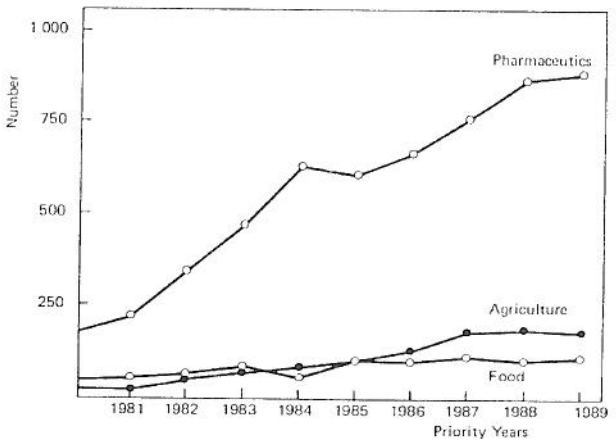

Fig. 3. Biotechnology patents at the EPO – production branches *(6)*
Slika 3. Patenti iz biotehnologije u EPO – područja proizvodnje *(6)*

the Biotechnological Faculty and industrial institutes, there came a stagnation in the application of biotechnological processes and products due to obstacles including market size, industrial infrastructure and availability of financial resources.

In the period 1984–1989 Pliva filed 65 patent applications, five of which concern processes or products of biotechnology (7). According to the programs of investment, biotechnology will occupy an important place in the economic development of the Republic of Croatia.

Although many factors are still preventing biotechnology from fully realizing its competitive potential, rapid advances at the scientific and technological frontier, a steady stream of secondary innovations contribute to our belief that biotechnology will become a major social and economic force in the coming century.

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