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REVIEW ARTICLE

Patentability of Animal Models: India and the Globe

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ABSTRACT

Patents and related issues began to ring a bell in research world years ago. Conceptual and theoretical property including new appliances also never new to pharmaceutical industry. But the tug-o-war between the traditional and modern themes remained as it is. Novel therapeutic application of newly invented procedure or instrument also added to think over again about animal models in pharmacy hub for various purpose of research. Transgenic animal's patent law ideally entered in to a market in 1987. Although it seems easy but rather it was heavy task to develop such disease models which might have taken a quantity ranging from several to many in terms of time, money and human resources. In India animal models are not yet patentable unlike developed countries. In order to use such animal models they should have a close similarity to human organism which will convey the likeness or replica of the pathological entity and its various medians. Transgenic animal disease models are animals that have been genetically altered to have traits that mimic the symptoms of specific human pathologies. In certain inventions such as AIDS mouse as an animal used lack the receptor and co receptor that allows them to be infected with HIV. The mice were genetically altered to contain the gene for human CD4 promoter upstream of the human CD4 gene and human CKR-5 co-receptor gene. Similarly there are different models such as Alzheimer mouse, oncomouse, and smart mouse were also evolved accordingly.

Keyword: Animal Model, Ethics, India, Patent.

INTRODUCTION

A patent is in the form of industrial property, or as we commonly know an intellectual property. A patent is a monopoly right granted to a person who has invented a new and useful article or an improvement of an existing article or a new process of making an article. It consists of an exclusive right to manufacture the new article invented or manufacture an article according to the inventive process for a limited period [1]. The fundamental requirements for obtaining a patent are lay down in four sections of Title 35 of the U.S. Code: 101, 102, 103, and 112. An important facet of patent protection is the exchange of information [2]. The inventor must describe the know-how related to the invention. This allows other scientist to think upon the invention for experimental purposes, thereby facilitating a continuous flow of inventions. After the lapse of period of patent protection, the previously protected information and technical known how falls into the public domain. According to the World Intellectual Property Organization (WIPO), patent is an exclusive right granted for an invention, which is a product or a process that provides a new way of doing something, or offers a new technical solution to a problem [3]. In order for an invention to be eligible for patent protection, it must meet the following criteria: novelty, inventive step and usefulness. The novelty requirement necessitates some new characteristics not known in the body of existing knowledge, termed as prior art, in its technical domain. The invention must exhibit an inventive step, which requires that it must not be obvious to a person with ordinary skill in the arena [4]. To meet the usefulness requirement, an invention

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must be of a kind which can be applied for practical purposes.

Requirements of Patentability:

Section 101 of the Act states that whoever invents or discovers any new or useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent. Thus, a patentable invention should be a process, machine, manufacture, or composition that is a new and useful improvement upon the prior art. Section 102 of the Act mentions the novelty factor. In brief, novelty means that the invention was not and could not have been known by someone other than the inventor before the inventor filed an application. The invention could have been known if it was printed in any publication including patent applications in any country. Another requirement of section 102 is utility, which contains encompasses three discrete requirements. First, the invention must be operable or capable of use (general utility). Second, it must solve the problem it is designed to solve (specific utility). Third, the invention must have a minimal social benefit and not be merely harmful or deleterious (beneficial utility) [5].

Section 103 of the Act further state that, a patent must not be granted if the subject matter as an entity would have been obvious. The matter must not be obvious to a person skilled in the art. Non obviousness may be a more difficult hurdle to overcome for patentability than the utility and novelty requirements because it demands that the invention must included a technical novelty. The technical steps must have certain degree of significance. An applicant must show that the differences between the subject matter which he decide to be patented and the prior art. In determining non obviousness, a considers: a) the scope and content of the prior art; b) the differences between the prior art and the claims and c) the level of ordinary skill in the perticular art [6]. According to section 101 of the Act, the invention must either be a process, a machine, or a composition of matter. Section 100 of the Act defines process as art, or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material. A process can be patented, even if the resulting product cannot. A machine is defined as "every mechanical device or combination of mechanical powers and devices to perform some function and produce a certain effect or result". A manufacture is the production of articles from raw or non-raw materials by transforming them into new forms, characteristics, qualities or concatenating them in a new fashion, regardless of whether it is done by hand or by machine. To be patentable, an inventor must meet the directions lay down in section 112 of the Act [7]. The purpose of the enablement condition is to facilitate the teachings of the patent so that they may be repeated easily without wasting resources. Section 154 describes the rights granted to the person under an issued patent. The patentee receives the right to exclude others from making, using, offering for sale, or selling the invention [8].

Animal Model:

An animal model is a living, non-human animal used for research and investigation of human disease, for the purpose of better understanding the disease without the added risk of causing harm to a human being during the entire drug discovery and development process. Many drugs, treatments and cures for human diseases have been developed with the use of animal models. Animal models representing specific pathological condition in the research and study of developmental processes are also referred to as model organisms [9, 10].

Animal models serving in research may have a genetically and chemically induced disease or injury that is akin to a human condition. These test conditions are often termed as animal models of disease. The use of animal models allows preclinical researchers to develop drug against disease which would be impossible in a human patient [11].

In order to serve as a useful model, a modeled disease must be similar in pathophysiology of human disease [12]. Animal models are used to understand more about a disease, its diagnosis and its treatment. An animal model is a mimic, likeness or image of a pathologic condition or disease entity of animals including humans which is present in a particular animal [7].

Types of Animal Models:

There are three types of laboratory animal models which are mentioned in the literature. They are spontaneous, induced and transgenic. Spontaneous models shape up as a result of naturally occurring mutations. Such disease models have been identified, characterized and preserved for investigative purposes. Induced models are produced by laboratory procedure like administration of a drug or chemicals, feeding of special diets or surgical procedure. The third category includes transgenic models. Transgenic animal models are created by the insertion of a particular human DNA into fertilized mouse oocytes which are then allowed to develop to term

by implantation into the oviducts of pseudo pregnant females [13]. Hence, animal models seem to open a new chapter in the issue of patentability. It has close liaison with the patentability of the bacteria or the transgenic animals [14]. The patentability issues of micro organisms and biotechnology derived animals seem to be the next topic of debate in the field of intellectual property [15]. This debate may be resolved if the animal model of a particular disease is considered to be a research tool.

Research Tool:

Research tools described as any tangible or informational inputs which are indispensable in the process of discovering a drug, a medical therapy, a diagnostic method, or a new crop variety. In brief, anything that a researcher needs to use or access in during the research-such as an assay, a genomic database, an animal model, crop germplasm and so on-may be christened as a research tool. Research tools are defined by the U.S. National Institutes of Health (NIH) as the full range of resources that scientists use in the laboratory, including "cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and drug targets, clones and cloning tools (such as PCR), methods, laboratory equipment and machines, databases and computer software, genes and gene fragments [16]. However before deciding the patentability of the animal model it is necessary to investigate the patentability of life forms. The reason behind this is the fact that all the animal models are actually life forms which have been transformed by the use of chemicals, administration of micro organisms or subjected to complex surgical procedures into a diseased animal.

The patents granted in life sciences so far:

Lious Pasteur received the U S patent no 141072 for yeast in the year 1873. First genetic engineering patent application filed at the EPO EP 1929. Plasmid for recombinant production of protein, e.g. insulin, in bacteria. Today, molecular biologists can not only identify these sequences and decipher their biological function, but also modify or clone one genotype, isolate individual genes and also ship them to bioreactors. More of biotech patents are directed to specific proteins and the DNA that codes for the protein. Important breakthroughs have resulted in genetic engineering with some of them being granted patents also like Cloned sheep, Genetic modification of mouse to make it susceptible to breast cancer and, therefore, particularly suitable for testing cancer drugs [17-19]. The invention was granted a US patent (4,736,866) in 1988 to Leder and Stewart of Harvard College. This patent had 12 claims and was licensed to DuPont. Tracy, a sheep whose germ line contains a genetic construction comprising a human gene plus 'promoter'. Tracy's milk glands produce proteins identical to humans. Proteins that can be extracted are human insulin, tissue plasminogen activator and alpha antitrypsin-a drug for treating mucoviscidosis[20].Patentable items include Methods and uses of biotech-related products: – producing a protein, PCR, in vitro diagnosis, in silico screening, preparation of plants and animals-making foods, medicines. Non patentable items include therapeutic or surgical methods on humans or animals. Plant or animal varieties as such-plant varieties protected by special system (UPOV Convention) essentially biological processes (standard breeding processes) for producing plant or animal varieties.

The current law:

Patentability of biological material:

The EPC allows patents for inventions that are new, involve an inventive step and are capable of industrial application (including agriculture). There is some specific exclusion from patentability but none that affect biological materials in general. Discoveries, as such, are unpatentable and this exclusion has been argued by opponents of biotechnology.

Plant and animal patents:

Article 1:

In Article 53b of the EPC, the patenting of plant and animal varieties is prohibited, as also are 'essentially biological processes for the production of plants and animals. It was held that, because new plant varieties were protectable under plant-breeders' rights, the exclusion from patentability should not extend more widely than to plants at the varietal level [21-22]. However, a recent decision of an EPO Appeal Board has cast doubt on the certainty of this simple solution of the problem of the 'interface' between the two legal systems. This decision is causing a problem for the EPO in its consideration of pending patent applications for transgenic plants and animals. In the domain of animal breeding, there is absence of system equivalent to plant variety rights. No definition of an 'animal variety' has ever been proposed in history. In the Harvard College Oncomouse patent application, the EPO Examining Division originally opened that no patent protection at all for animals was possible

but the EPO Appeal Board fortunately over-ruled this very close interpretation [23].

Articles 2 and 3:

Biological material is defined in Article 2 as 'any material containing genetic information and capable of reproducing itself or being reproduced in a biological system'. Article 3 states that this may include material isolated from its natural environment or produced by application of a technical methodology. This last statement provides important confirmation of the validity of existing practices of the European, US and Japanese Patent Offices, which have for many years treated purified and isolated natural products as patentable [20].

Article 4:

The plant and animal varieties are excluded from patentability by Article 53b of the EPC.

Article 5:

It lay down the following directives:

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, cannot be patentable inventions.
2. An element isolated from the human body or otherwise produced by means of a technical process, such as sequence or partial sequence of a gene, may be termed as a patentable invention, even if the structure of that element is identical to that of a natural element.
3. The industrial application of a sequence or a partial sequence of a gene must be describe in the patent application. One section of the article describes the possibility of patenting substance isolated from body or produced technically. A cell line or gene could hardly be useful without being isolated from the body or reproduced by a technical process (cloning) and hence should be patentable. Another section of this article is regarding patentability of gene fragments possessing specific biological function [24].

Article 6:

The following particular shall be considered unpatentable:

A. Processes for cloning human beings.
B. Processes for modifying the germ line genetic identity of human beings.
C. Uses of human embryos for industrial or commercial purposes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

Patentability of Human Stem Cells:

A complete human body is not patentable. An element isolated from the human body can be patentable even if it similar to natural element. The European Biotechnology Directive states that although neither the human body, nor any of its elements, can be patented, an element 'isolated from the human body or otherwise produced by a technical process, including the sequence or partial sequence of a gene' might be patentable. With the advent of seismic changes in biotechnology all the animal models are actually transgenic animals and hence it is important for a scientist to delve into the basics of transgenesis [25].

A transgenic animal is an animal that has been genetically altered so that it will produce a specific protein [26]. Foreign DNA has been inserted into the animal's DNA so it will produce a protein it does not normally have. They can be used for studying human diseases that the animals are not normally susceptible to, and can have strong medical benefits. The foreign DNA can be inserted in a number of different ways. It can be inserted by microinjection into a fertilized egg, where the DNA sequence is injected directly into the male pronuclear, or it can be created by delivering DNA in vitro to ES cells, then the ES cells are grown to the blastocyst stage and inserted in the uterus of a surrogate mother. Adding and deleting genes in these animals provides them with new properties that make them useful for better understanding disease or manufacturing a cure [27].

Transgenesis in animal models:

One of the most common uses of transgenic animals is to mimics human disease. Because the testing of new vaccines and drugs must first be performed on animals, animal disease models are indispensible. Yet many human diseases do not occur in animals, especially those animals convenient to work with like mice, so transgenic animals are created to mimic some aspect of human disease. A gene deficiency is created so that the animal is more susceptible to a disease, or genes can be added to get the same result [28].

Examples:

Transgenic Disease Models:

Transgenic animal disease models are animals that have been genetically modified to have traits that mimic the symptoms of specific human pathologies. The disease models are needed so

that we can decipher the disease for development of drug discovery [29]. Many animals do not normally exhibit the equivalent of certain human diseases. Hence a human transgene specific to the disease is expressed in the animal [17, 30]. This causes pathological characteristics of human in the animal so that it can be studied. Animal disease models are very useful in that they allow us to screen drugs that may be harmful or have bad side effects [31]. Once the therapeutic agents have been screened and tested, human cell line may then be tested, followed by healthy and diseased human test subjects in clinical trials [32]. But because it is not ethical or safe to perform the initial tests in humans, we use transgenic animals are used.

AIDS Mouse:

This animal is a mouse that was used for studying human immunodeficiency virus or HIV. The mouse has a transgene that encodes for the genome of type 1 HIV [33]. Mice normally lack the receptor and co receptor that allows them to be infected with HIV. The mice were genetically altered to contain the gene for human CD4 promoter upstream of the human CD4 gene and human CKR-5 co-receptor gene. The production of the co-receptors in the mice allows for the HIV virus to attach to the T cells. The mouse then has the ability to synthesize all the viral proteins that aid the HIV in successfully infecting it [32].

The AIDS mouse was designed to exhibit symptoms similar to human AIDS such as wasting, atrophic lymphoid organs, atrophic kidneys, and early death. Studying these mice has led to the identification of human host factors that play crucial roles in the type 1 HIV replication cycle [32, 34]. Thus, these studies have not only contributed towards our basic understanding of type 1 HIV life-cycle, they have also provided us with new targets for future therapeutic intervention.

Alzheimer's Mouse:

Alzheimer's is a disease marked by the loss of cognitive ability, and associated with the development of abnormal tissues and protein deposits in the cerebral cortex. It is a neurological disease that affects the memory [35]. The impairment to the brain is due to the accumulation of neurotoxic precursors to and builds up of amyloid proteins, which form a plaque in the brain. The amyloid-beta protein is initially soluble (and highly toxic to neuronal cells), and itsbuildup eventually causes the degeneration of neurons and their neurotransmitters in the brain [35]. Expression of a mutant version of human amyloid precursor protein (APP), mRNA, holo-APP and A-beta in the brains of the mice (which are associated with anaggressive early onset type of Alzheimer's disease) causes them to exhibit human-like Alzheimer's disease symptoms [35, 36]. Alzheimer's mouse models express high levels of human mutant Q-amyloid precursor protein, and the animals progressively develop many of the pathological hallmarks of Alzheimer's disease [35-37]. The mice also develop neurofibrillary tangles. The mouse model develops many of the neuropathological symptoms of AD in a temporal and regional dependent manner. This model has been very useful for AD research. The Alzheimer's mouse in one experiment developed most of the pathologic changes se en in human brains with the exception of neurofibrillary tangles. What makes this model an ideal candidate for ethical acceptance is that the mice do not suffer to any measurable degree, yet this model is essential for continuing research into Alzheimer's therapeutic compounds. This observation may cause a reconsideration of the pathogenesis of the disease, suggesting that these tangles are a result of a destructive neurological process rather than a direct cause [35]. The vaccine restored neurological performance in the mice, and is currently in phase II human clinical trials at Elan Pharmaceuticals.

Oncomouse:

It was first animal to ever be patented [39]. Oncomouse has been genetically engineered and fabricated to develop specific forms of cancer [40]. This mouse's germ cells and somatic cells contain an activated human oncogene sequence that has been introduced into the animal at an early embryonic stage to ensure that the oncogene is present in all the animals' cells. This increases the chances of the mouse developing malignant tumors, so it can be used to test various potential anti-cancer treatments [30].

Oncomice have been created that carry either the v-Ha-ras or the c-myc gene driven by the mouse mammary tumor virus (MMTV) promoter/enhancer [28, 42]. These to genes are important for cellular growth. When these two mouse strains are crossed, the mouse develops accelerated tumor formation in its cells. Potential anti-tumor compounds can be tested on the animals to see if the animal has any sign of reduced carcinogenesis.

Smart Mouse:

Although not a disease model, this animal was used as a model for what could be done to help memory loss in humans. Joe Z. Tsien, a researcher at Princeton University, genetically engineered a

smart mouse. He named the mouse "Doogie" after the boy genius in the TV series Doogie Howser, MD [42]. Doogie was able to navigate through mazes better than regular mice, and has shown signs of better intelligence and memory through other tests. This strain of mice also retained into adulthood certain brain features of juvenile mice, which, like young humans, are widely believed to be better than adults at grasping large amounts of new information. Research has reviewed that in young animals memory is triggered even when the input signals are relatively far apart. This use of transgenic animals is ethically debatable. Even if this experiment is not performed in humans, it is very useful in the study of memory. It shows that some day we may be able boost human intelligence and it could be used in gene therapy for such areas as dementia.

Diamond vs. Chakrabarty:

In 1972, microbiologist Ananda M. Chakrabarty applied for a patent application for his invention of a genetically engineered bacteria created by adding two different plasmids to the wild-type organism, each of which provided a separate pathway for breaking down components of crude oil. Patent usefulness requirement was achieved by the bacteria's immense role in the treatment of oil spills. Novelty was also shown as there are no naturally occurring bacteria with the same capabilities. The non-obvious requirement was obvious. When a patent examiner initially rejected Chakrabarty's claim for the bacteria on the grounds that transgenic microorganisms were products of nature and not patentable, the scientist appealed and took his case to the Supreme Court where Diamond vs. Chakrabarty became a mild stone case in patent law. The court discovered that the claim achieved all three requirements set forth under section 101. Chakrabarty was granted patents for the bacteria themselves in addition to exclusive rights for the method of producing it [43].

Animal Patents:

The first animal patent, on the Harvard oncomouse, was awarded in 1988 just one year after the Patent Office affirmed that creatures may be protected under patent law. The oncomouse is a mouse given the human ras gene which makes susceptible it to cancer with much greater frequency than unmodified mice [40]. Till September 21, 2003 there have been 454 animal patents issued in the United States, of which over half (54%) are designated as disease models [6]. In addition to the oncomouse, some other mouse models that have been patented include an Alzheimer's mouse [31]; a model for Kaposi's sarcoma [17] and an HIV mouse (incapable of viral transmission).

Other animals to receive patent protection now include cows, sheep, pigs, birds and fish, as well as macaques and chimpanzees [6, 7, 13, 15, 44, 45]. In addition to patents for animals themselves, new techniques and technologies that enable scientists to gain more power over animal genomes are being protected by patents. For example, Avigenics Incorporated has been awarded patents on a "Windowing Technology" for creating an aperture through egg shells which enables the creation of transgenic chickens, certain to be valuable in both food and drug production markets [46]. As more and more transgenic applications are discovered, the number of biotechnology patents on animals is sure to surge.

General Patentability Issues:

In granting patents to inventors, the U.S. Patent and Trademark Office requires that a submission satisfy the three requirements of novelty, utility and non-obviousness (35 U.S.C. 101, 102, 103). None of the requirements demands that the invention be inanimate or non-living. Title 35 United States Code 101 states that "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent thereof, subject to the conditions and requirements of this title" [4].

Oncomouse Ethics:

The oncomouse is one of the most controversial transgenic animal models in use today. By incorporating an activated oncogene sequence into the germ cells of a mouse, researchers hope to ascertain more about carcinogenesis and cancer formation [39]. Obtaining a more complete understanding of what causes cancer and being able to test anti-cancer drugs in mice represent strong medical benefits. But the ethical concern with the oncomouse is that it usually suffers in order to collect relevant information, which is in opposition to the principles of animal rights [47]. It becomes necessary to consider the moral implications of producing such a species as well as measures of reducing animal suffering [30]. Other categories are duration of distress, duration of the experiment, and number of animals per experiment. The idea is to deliberately create tension between the two opposing positions [48]. Once a system has been set up to regulate experimentation, methods can be found that minimize animal suffering like administration of painkillers and sacrificing the animal before severe damage can be done. Human and animal

ethics require that the oncomouse be used cautiously and sensibly in research.

Positive and negatives for patenting animals:

Positive for patenting animals:

Patenting of animals models is need of hour, because it is an indispensible tool for screening of novel molecule to various diseases. Human pathological condition in an animals is of at a most important to determine the therapeutic efficacy of novel molecule. A suitable animal model which mimics the human condition is a boomed to drug discovery [14]. They allow the facilitation of the screening process to ultimately eliminate the inactive chemical and biological moieties and assess the pharmacologist to identify the therapeutic potential and characterize the toxicological profile of novel chemical entities or novel biological entities. A animal model suitable for screening a wide variety of drug allows optimum utilization of resource as various facets of the diseases are expressed in the animals which if reversed are discernibly visible by the scientist. Transgenic animals and spontaneous diseased animals are better flag bearer of disease [39]. They expressed symptoms akin to human beings. An array of chemical when administered to animals develops disease condition. Several complex surgical procedures enable the scientist to produce typical pathobiological condition in the animals. In the light of such exciting and innovative field it is obvious that animal model should be granted patents provided they follow the condition lay down by US PTO.

Negatives for patenting animals:

The drawbacks of patenting of animal models are sparse. The two major flaws in granting the patent to animal model are: 1. Morality 2.Reproducibility of model in different experimental condition.

1. Morality: The issue of animal ethics and cruelty to animals is a bone of connection between the scientific community and animal well fare activates. However, it is obvious that preclinical animal models are an important step in drug discovery, because they lay the fundamental for human trials. Moreover, most of the studies are conducted on rodents on under controlled experimental condition which complies with the guideline lay down by CPCSEA.
2. Reproducibility: Animal models once established can be reproduced in the same species if the procedures are closely adhered. However, minor discrepancies may arise as animals are biological entities and not mechanical systems. This flaw has been bridge by an advent of genetically engineered animals which invariably exhibits the required pathological conditions.

The Indian Scenario:

In India the Indian Patent Law section 3i and 3 j states that all the surgical processes and animals are not patentable [49, 50]. Hence animal models are not patentable in India. Inventions pertaining to microorganisms and other Biological material were subjected to product patent in India unlike many developed countries. But with effect from 20.05.2003 India has started granted patents in respect of invention related to microorganisms though India was not obliged to introduce laws for patenting microorganisms per se before 31.12.2004. Microorganisms patenting per se being considered to be a product patent the period of protection was 5 years from the date of grant or 7 years from the date of filing of application for patent. Now grant of patents for microbiological inventions is for a period of 20 years from the date of filing. The problem in this aspect of the law is that with seismic changes in the overall process of drug discovery US patents of animal models encourages scientists in USA and Europe to produce animal models which are very close to human disease and hence contribute significantly to the process of drug discovery. If the suitable amendments are made then animal models can be patentable in India and hence it would open novel vistas in research arena in India.

CONCLUSION

Protection of laboratory animals has been regulated by the Animal Welfare Act, but activists have complained that by not covering mice, rats and birds, the 51 Act is basically useless because 95 percent of lab animals consist of these warm-blooded, species. Patent law entered the biotech market in 1987 when it issued a statement claiming its authority to grant patents on transgenic animals. The famous oncomouse case ensued which was widely debated, and even rejected in Europe and Canada before receiving patent protection in the former market. Arguments that patents for creatures are not moral, hurt family farmers and could lead to patenting humans do not stand up to reason. The fact is, patents provide a means of compensation for the companies that invest millions of dollars in research which in turn stimulates further research and eventually better treatments. The benefits of

patenting transgenic animals thus outweigh the risks.

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