

## Patenting of Genetic Inventions

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The genetic inventions in the patent system are similar to chemical inventions. Genetic inventions that are patentable include genetic materials such as DNA, RNA, cDNA, EST's (Expressed Sequence Tags), SNPs (Single Nucleotide Polymorphs) and recombinant vectors. These inventions need to satisfy the criteria of patentability such as novelty, non-obviousness, utility, enablement and sufficiency of disclosure. The utility standards for genetic inventions are higher than for other inventions. The USPTO has issued guidelines for the utility requirement with respect to genetic sequences. These have been further clarified by recent court decisions in the US. One of the issues relating to patenting of genetic inventions revolves around the question whether a DNA sequence is a discovery or an invention. In Europe, the recently issued directive on biotechnology clearly distinguishes between a discovery and an invention. The Directive makes it clear that genes or other biological elements which are isolated from their natural environment and having a technical effect are patentable. This article discusses most of the issues relating to patenting of genetic inventions.

**Keywords:** ESTs, SNPs, recombinant vectors, microorganism, recombinant DNA technology

Biotechnology may be defined as the application of science and engineering in the direct use of living organism or parts or products of living organisms in their natural or modified forms.<sup>1</sup> Biotechnology encompasses the application of all biological systems, which include whole cells, tissues, organelles or enzymes derived from animal and plant cells, as well as microorganisms.<sup>2</sup> Biotechnology further deals with recombinant DNA technology, which can be used to modify the genetic material of living cells to produce new substances or perform new functions. The biotechnological inventions in the patent system are similar to chemical inventions. These include inventions, which are biological, microbiological, genetic engineering, medical, and agriculture. The biotechnological inventions are not limited to developments in the area of genetic engineering but extend to biologically active compounds from microorganisms, plants, insects and animals. This paper deals with the patent protection in the area of DNA, RNA and gene sequences in different countries. It makes business sense to apply for patents relating to genetic inventions. Several thousands of applications have been filed worldwide for genetic inventions.

### TRIPS and Indian Patent Law

India has amended the Patents Act, 1970, three

times in a span of five years (between 1999 and 2005). The first was in the year 1999,<sup>3</sup> to give effect to the provisions of the TRIPS and thereby meet the first deadline, and some of these provisions were made retrospective from 1995. The second amendment was made in 2002<sup>4</sup> and brought the Indian law in substantial compliance with the Agreement. The third amendment was brought about in December 2004, which came into force from 1 January 2005;<sup>5</sup> to make the Patents Act fully TRIPS compliant. The deletion of Section 5<sup>6</sup> of the Indian Patents Act, 1970 was important to allow product patents in the area of biotechnology, chemicals and pharmaceuticals.

Article 27(1)<sup>7</sup> of the TRIPS Agreement clearly states that patents should be granted for inventions in any field of technology without discrimination, subject to certain clauses. This implies that biotechnological inventions are patentable subject matter. The patenting of genes and/or DNA sequences is popular in the US, the European Union (EU) and Japan. However, patenting of genes/DNA sequences *per se* was not allowed in India until January 2005, but processes involving recombinant DNA technology to produce proteins involving a gene or DNA sequence was patentable subject matter. Product patents for DNA, RNA or genetic inventions are patentable subject matter from January 2005 following the third amendment.<sup>5</sup>

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### DNA/RNA Sequences

A gene is a structural unit of inheritance in living organisms. It is a segment of DNA that has a particular purpose, *i.e.*, it codes for a protein or a specific enzyme. The strands of DNA on which the genes occur are organized into chromosomes. Each gene of an organism provides a blueprint for the synthesis (*via* RNA) of enzymes and other proteins at a specific time. Genes govern both the structure and metabolic functions of the cells, and thus of the entire organism. Genes located in reproductive cells pass their information to the next generation. A gene is the DNA that encodes the primary sequence of some final gene product, which can be either a polypeptide or an RNA with a structural or catalytic function.<sup>8</sup>

Patenting of DNA and genes sequences is a broad term that refers to the patenting of a process that involves identification, isolation of DNA or associated materials like RNA as well as chemical substances related to DNA such as proteins, and peptides. The genetic materials that can be patented include genes, DNA sequences, cDNA, ESTs (Expressed Sequence Tags) and SNPs (Single Nucleotide Polymorphs).

The DNA related inventions may include one of the following:

- mRNA (messenger RNA) which is encoded by the DNA to express a protein;
- cDNA (complementary DNA), that is a DNA without introns matching the sequence of the mRNA, which provides the exact DNA sequence of the expressed protein;
- isolated and purified DNA sequence such as genomic DNA coding for a gene, or a fragment thereof;
- oligonucleotides;
- Proteins or polypeptides;
- DNA markers;
- Recombinant (genetically modified) DNA including recombinant plasmids or recombinant vectors;
- Genetically modified organisms such as genetically modified bacteria, fungi, plants and animals.

The basic criteria for a patent to be granted are novelty, non-obviousness (inventive step) and utility. For a patent to be granted in India it should not be covered in the negative list in Section 3<sup>9</sup> which provides an extensive list of what are not inventions (exclusions) under the Indian Patents Act. The

inventions related to DNA molecules or sequences must not be contrary to public order and morality.<sup>10</sup>

The US Courts and EPO have granted patents to genetic inventions, however, the issue of patentability of genes and gene sequences is yet not settled. A number of arguments are advanced against the patentability of genes, which are given below:

- Genes are naturally occurring and not new;
- Genes are basically discoveries, *i.e.* the invention claimed is actually a disclosure of something already in existence; and
- The process involves gene isolation and cloning, which are well known processes and hence no inventive step is evident in the claimed invention.

Despite these arguments, various genetic inventions have been granted patents by USPTO and EPO. In the case of *Amgen Inc v Chugai Pharmaceuticals*,<sup>11</sup> an 'isolated gene' was held to constitute patentable subject matter. In EPO case of *Howard Florey/Relaxin*,<sup>12</sup> it was held that purified copies of genes produced by technical processes outside the body are patentable. In 1998, the EC issued a directive called *Biotechnology Directive*<sup>13</sup> to clarify matters related to patentability of biotechnological inventions. Article 5 of the directive states:

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 constitute patentable inventions.
2. 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, may constitute 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 disclosed in the patent application.

Another condition for patentability of inventions requires it to be a product of human invention. This is perhaps the most controversial aspect of the 'patenting of life' debate. The issue revolves around the distinction between an invention and a mere discovery. For instance, the patent would not be granted for a naturally occurring mineral or some known element because they are pre-existing products of nature. However, an individual who creates a product from such discoveries may correctly be given credit for being the inventor of something new.

An important exclusion in Section 3(c)<sup>14</sup> of the Indian Patents Act is that the discovery of an invention is not patentable subject matter. Therefore, the question of whether a DNA sequence is a discovery or an invention must be addressed first. This is based on a assumption that genes are naturally occurring, these are discoveries, and not inventions. We do not have any case laws in India regarding discovery. In Europe also ‘discoveries’ are not patentable subject matter.<sup>15</sup> There are not many case laws in Europe either. The EC has, however, issued directives and guidelines regarding discoveries. Hence, the position relating to ‘discovery’ under the European Patent Convention are discussed below.

Article 3.2 of the Biotechnology Directive of European Union states that ‘Biological material which is isolated from its natural environment or produced by means of a technical process maybe the subject of an invention even if it previously occurred in nature’.

The guidelines for the examination in the European Patent Office were revised in February 2001<sup>16</sup> which reads: ‘To find a previously unrecognised substance occurring in nature is also mere discovery and therefore un-patentable. However, if a substance found in nature can be shown to produce a technical effect it may be patentable. An example of such a case is that of a substance occurring in nature which is found to have an antibiotic effect. In addition, if a microorganism is discovered to exist in nature and to produce an antibiotic, the microorganism itself may also be patentable as one aspect of the invention. Similarly, a gene which is discovered to exist in nature may be patentable if a technical effect is revealed, e.g. its use in making a certain polypeptide or in gene therapy’. Further, Rule 23(c) of the EPC states that ‘Patentable biotechnological inventions shall also be patentable if they concern: (a) biological material which is isolated from its natural environment or produced by means of a technical process even if it previously occurred in nature...’

The guidelines and rules of the European Patent Office clarify that DNA or gene sequences are patentable subject matter as these are considered synthetic molecules isolated from the organisms and characterized and produced as recombinant molecules or synthetic molecules containing the information as in the natural genes.

The position in the US regarding discovery is different as compared to India and Europe. In the US law, Section 101 reads ‘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 there for, subject to the conditions and requirements of this title’. In the case of *Funk Brothers Seed Co v Kalo Inoculant Co*,<sup>17</sup> the patent involved a process for inoculating leguminous plants with strains of naturally occurring bacteria to allow the plants to fix nitrogen from the air. Wherein the Court laid down that, claimed inventions are a ‘discovery of the phenomena of nature,’ and therefore genes should not be patentable. A gene is not an ‘invention’ in the same sense that a machine is an ‘invention.’ However, while the Court never explicitly overruled *Funk Brothers*, it limited its holding in a subsequent decision.

In *Diamond v Chakrabarty*,<sup>18</sup> the Court held that bacteria, which had been genetically modified to degrade oil, could be patented. The distinguishing factor in *Chakrabarty*, as compared to *Funk Brothers*, appeared to be that in *Chakrabarty*, the bacteria had been altered by human intervention, furthermore the bacteria was considered to be an invention as it had two energy generating plasmids which is quite different and uncommon for the existing bacteria. In light of these cases, how would the Court analyse a challenge to the patenting of genes? A gene isolated for patenting is not altered in the same way as the bacteria in *Chakrabarty*, but it is purified and amplified. The Court has never answered whether this distinction is sufficient to qualify a human gene as patentable subject matter. However, the 35 USC 101,<sup>19</sup> is the pertinent statute which allows grant of a patent to a person who ‘invents or discovers’ a new and useful composition of matter, among other things. Thus, an inventor’s discovery of a gene can be the basis for a patent on the genetic composition isolated from its natural state and processed through purifying steps that separate the gene from other molecules naturally associated with it.<sup>20</sup> This opinion of the USPTO corresponds to case law subsequent to *Funk Brothers*, which ‘seems to represent the high-water mark in the ‘products of nature’ doctrine.’ For example, in *In re Bergstrom*, the Federal Court of appeals held that scientists could patent purified forms of two human hormones called prostaglandins because the purified forms do not occur naturally.<sup>21</sup>

### Criteria for Patenting of Biotechnological Inventions

The recent amendments to the Patent Act have incorporated many important changes that have a

significant bearing on the patent law in India. The definition of the term 'invention' was amended as in Section 2(1)(j)<sup>4</sup> which reads as 'a new product or process involving an inventive step and capable of industrial application'. The term 'inventive step' is defined in Section 2(1)(ja),<sup>5</sup> which states that 'inventive step means a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art'.

The three basic requirements for an invention under Indian law are:

- It should be new (novelty);
- It should involve an inventive step (non-obviousness of the invention); and
- It should be capable of industrial application.

#### Novelty

Novelty is the first requirement that needs to be fulfilled. Section 2(1)(j) of the Indian Patents Act requires the invention to be new, that is, it must be different from 'prior art'. That is, it should not have been published anywhere in the world before the date of filing of the application. In addition, subject to certain exceptions provided in the Patent Acts of the countries concerned, it should not have been publicly used or demonstrated before filing. This signifies that the work that requires patent protection should not form a part of the public domain, prior to the filing of patent application. The US grants inventors one year grace period for public disclosure before grant of patents.<sup>22</sup>

The criterion of novelty with regard to genes and gene products is easily met, since they are considered chemical entities, and these can be patented in most patent offices if they are purified and isolated from the form in which they occur in nature. In most countries, a claimed gene is considered novel if the claim covers the isolated and purified gene. The applicant must be able to prove that the existence of the gene was not known and that he was the first to isolate it, characterize it and define its utility. This implies that while genes are not patentable *in situ*, purified copies produced by technical processes outside the body are patentable. (Howard Florey/Relaxin Case).

#### Non-Obviousness

An invention that is non-obvious means that it would not have been entirely obvious to a person

skilled in the field to have created the invention taking into account the current state of knowledge in that field.<sup>23</sup> Section 103 of the US Patent Act defines non-obviousness as when 'the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.' Non-obviousness in the field of biotechnology patents is a fact-intensive determination where potential success in experimentation and new properties of the invention carry significant weight.

While the USPTO (United States Patent and Trademark Office) often makes the determination as to whether an invention is non-obvious, the standard is actually set by the Courts and is only applied by the USPTO. The Courts can overrule the USPTO in litigation.

An invention in biotechnology is obvious if the prior art provides motivation for the invention and enables one of skill in the art to invent with a 'reasonable expectation of success'.<sup>24</sup> In 1996, the Supreme Court in *Graham v John Deere Co* articulated four factors to determine non-obviousness.<sup>25</sup> The four factors include: (1) the scope and content of the prior art, (2) the difference between the prior art and the claimed invention, (3) the level of ordinary skill in the art; and (4) other secondary considerations. Secondary considerations may include commercial success; long felt but unsolved need; unexpected result; other's failure to solve the same problem.

The Court of Appeals for the Federal Circuit, in *In re Deuel*,<sup>26</sup> held that 'general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search'.<sup>27</sup> Hence, it was possible to obtain a gene patent using an obvious method.<sup>28</sup> Furthermore, even if the prior art provides the motivation for success and a 'reasonable expectation of success,' the exhibition of 'unexpected properties' will render an invention non-obvious.<sup>29</sup> Examples of unexpected properties are superior purity, specific activity, and unexpected yield.<sup>30</sup> In the case of *Hybritech Incorporated v Monoclonal Antibodies Inc*<sup>31</sup> wherein a suit was brought alleging infringement of US Pat No 4,376,110 for immunometric assays using monoclonal antibodies, the Court laid down that 'whether the

claimed invention would have been obvious at the time the invention was made is reviewed free of the clearly erroneous standard although the underlying factual inquiries--scope and content of the prior art, level of ordinary skill in the art, and differences between the prior art and the claimed invention--integral parts of the subjective determination involved in Section 35 USC 103, are reviewed under that standard. Objective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered before a conclusion on obviousness is reached and is not merely icing on the cake.'

Similar question was raised in the case of *Amgen Inc v Chugai Pharm Co*<sup>32</sup> wherein the Federal Circuit Court treated DNA as a chemical composition and applied chemical case law based on structural similarity when determining the non-obviousness of a DNA molecule. The honourable Court also stated that one must inquire whether the prior art would have suggested to one of ordinary skill in the art that Lin's probing and screening method should be carried out and would have a reasonable expectation of success, viewed in light of the prior art.' Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure.' However, because of the degeneracy of the genetic code, where more than one DNA sequence may code for a given protein, the Court has held that the prior art disclosure of a full or partial amino acid sequence does not necessarily render the DNA sequence coding for that amino acid sequence obvious.<sup>33</sup>

In *In re Deue*<sup>34</sup>, the Court found the existence of a general method of isolating DNA molecules to be 'essentially irrelevant' as to whether the specific DNA molecules would have been obvious without other prior art suggesting the claimed DNA molecules.<sup>34</sup> The Court stated that a case for obviousness is normally based on structural similarity between the claimed compound and a prior art compound.<sup>35</sup> Thus, the combination of a reference disclosing a partial amino acid sequence for a protein together with a reference teaching a general method of DNA cloning did not render DNA molecules coding for the protein obvious.<sup>36</sup> The redundancy of the genetic code meant that a great number of possible DNA molecules could have coded for the protein.<sup>37</sup> Hence, there was no motivation to prepare the specific DNA claimed.<sup>38</sup>

A gene, whether of human origin or otherwise, or a DNA sequence can thus be patented in isolated form

if that gene or sequence has not been described before, the isolation of that gene or sequence was not obvious, and that the gene or sequence has some utility. As it is difficult to identify a particular gene within the vast amounts of DNA that exists in a cell, a gene or gene sequence is also likely to meet the non-obviousness requirement. While it may be obvious to use well-known techniques to isolate DNA sequences in general, the isolation of a particular DNA sequence is not obvious.<sup>39</sup>

#### Utility

DNA sequences, such as genes, ESTs or SNPs, have a wide variety of applications. In many cases, there are known uses of DNA, like for producing proteins or diagnostics or in forensic sciences (DNA fingerprinting). However, there are also increasingly innovative uses for DNA, like the sensor developed by the University of Illinois at Urbana-Champaign that can detect lead using specially designed DNA.<sup>40</sup> Protein production is one of the most obvious uses of gene sequences, since DNA carries the information that codes for the protein sequence. These proteins may be structural proteins, hormones, enzymes, blood factors, antibodies, vaccines or antigens. The gene sequence carrying the information is cloned into a relevant host organism, and the organism is induced to produce the protein. Patented recombinant DNA technologies, which include production of human insulin-like growth factor (US Pat No 6,251,865). Similar examples are provided in Table 1.

The use of DNA sequences for (pre and post symptomatic) diagnostic testing requires, identification of the disease-causing gene(s), sequencing the gene and identifying the ESTs or SNPs that characterize the disease-causing nature of the gene and production of said DNA fragments. Once this knowledge is available, testing a patient's genome for the gene is made simple. However, since not all diseases are Mendelian (single gene) diseases, and since these identified genes may only predispose a person to the disease and not actually cause it, diagnostic testing of DNA must also be accompanied with pre and post-test counselling. Patented diagnostic tests are available for Diabetes (Harvard, University of Chicago), Canavan disease (Miami Children's Hospital), Huntingdon's disease (Massachusetts General Hospital), and inherited Breast Cancer (BRCA case), among others. The therapeutic uses of DNA include somatic gene therapy and DNA

vaccines. An example for this would be the treatment of X-linked severe combined immunodeficiency using somatic gene therapy.

The use of DNA as research tools is most pertinent for ESTs. ESTs are small regions in the active part of a gene, which can be labelled and used as a probe to locate that gene. It can provide valuable information as to the presence of that gene in a genome. These can be used as markers for genes, where they are tagged and hybridized with a fragment of DNA to identify the full length gene. They can be used in the process of chromosome walking, where long stretches of

DNA are mapped and sequenced. They can be used in microarray technology, where they are used to identify gene expression in different cells. In the 1990s, a number of patents were granted for sequences based on the fact that they were useful as research tools, but there was widespread opposition by several scientists. The argument against patenting of DNA sequences especially EST sequences is that since it has such little utility by itself, it should not be patentable. It carries only information, and as such has no practical utility. The counter argument, however, is that the utility of an isolated, purified, and

Table 1—Some DNA patents and excerpts from their abstracts

S.No.	Use of DNA sequence	Patent details	Assignee	Patent number
1	Protein production <ul style="list-style-type: none"> <li>Recombinant DNA technology to produce proteins in a host organism.</li> <li>Can be hormones, enzymes, blood factors, antibodies, antigens, etc.</li> <li>Process patent or product patent</li> <li>Can patent DNA sequence or protein.</li> </ul>	Insulin-like growth factor agonist molecules  Compounds are provided that inhibit the interaction of an IGF with any one of its binding proteins and not to a human IGF receptor. These IGF agonist compounds, which include peptides, are useful to increase serum and tissue levels of active IGFs in a mammal.  Process for preparing recombinant aprotinin and recombinant aprotinin variants having the natural N-terminal sequence  The invention relates to a process for preparing recombinant aprotinin and recombinant aprotinin variants having the natural N-terminal sequence, with the recombinant aprotinin and/or the recombinant aprotinin variants being present as homogeneously processed, secreted proteins.	Genentech Inc  Bayer-Aktiengesellschaft	US Pat No 6,251,865  US Pat No 5,707,831
2	Diagnostic testing <ul style="list-style-type: none"> <li>Pre and post symptomatic.</li> <li>Requires identification of disease causing gene/genes and sequencing the gene.</li> <li>ESTs/SNPs that characterize the disease causing nature of the genes.</li> </ul>	Detection of glucokinase-linked early-onset non-insulin-dependent Diabetes mellitus  The invention relates to a method for detecting a propensity to develop early-onset, non-insulin-dependent Diabetes mellitus.  Huntingtin DNA, protein and uses thereof  A novel gene, huntingtin, is described, encoding huntingtin protein, recombinant vectors and hosts capable of expressing huntingtin. Methods for the diagnosis and treatment of Huntingdon's disease are also provided.	ARCH Development Corporation  The General Hospital Corporation	US Pat No 5,541,060  US Pat No 5,693,757
3	Therapeutic use <ul style="list-style-type: none"> <li>Somatic gene therapy</li> <li>DNA vaccines</li> </ul>	Delivery system for gene therapy to the brain  A gene delivery system which is both safe and results in long-term expression throughout the brain has been developed. A lipid-entrapped, polycation-condensed DNA (LPD) system has been developed for brain gene delivery, using an adeno-associated viral ('AAV') vector.	Frank L Sorgi	US Pat No 6,436,708
4	Research tools <ul style="list-style-type: none"> <li>Molecular markers</li> <li>Microarrays</li> <li>Chromosome walking</li> </ul>	5' ESTs for secreted proteins expressed in brain  The 5' ESTs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. Upstream regulatory sequences may also be obtained using the 5' ESTs. The 5' ESTs may also be used to design expression vectors and secretion vectors.	Genset	US Pat No 6,222,029

sequenced gene goes beyond the information in its DNA sequence.<sup>41</sup>

The examination guidelines for patent applications relating to inventions in the field of chemicals, pharmaceuticals and biotechnology [Annexure 1, Manual of Patent Practice and Procedure, Patent Office (2005), India] states that gene sequences and DNA sequences are not patentable if functions (utility for the genetic inventions) are not disclosed. However, a lack of case laws in India requires to look at utility or industrial applicability requirements in other countries.

In the US, the *Brenner*<sup>42</sup> case resulted in the definition of the utility requirement for chemicals. Manson's patent claims included a steroid and the process for its production. However, he had not described its utility completely, but had shown it to be similar to other steroids that had anti-tumor properties. The patent examiners had denied this patent on the basis of lack of utility, and the Board of Appeals affirmed this decision, stating: 'It is our view that the statutory requirement of usefulness of a product cannot be presumed merely because it happens to be closely related to another compound which is known to be useful.' The Courts of Customs and Patent Appeals<sup>42</sup> reversed the decision and the Commissioner of Patents (Brenner) appealed to the Supreme Court.

The Supreme Court in *Brenner v Manson*<sup>42</sup> reversed the judgement of the CCPA, and laid down certain clauses for fulfilling the utility requirement. It stated, 'A process patent which is in the chemical field and has not been developed and pointed to the degree of specific utility creates a monopoly of knowledge which should be granted only if clearly commanded by statute.'<sup>42</sup> Moreover, they said an equitable exchange would be granting a patent for an invention with substantial utility whose benefit would be derived by the public. Unless the invention was refined and developed till it could point to substantial utility, the Court said it was not justified in granting a patent for claims in such a broad field.

*In Re Brana*<sup>43</sup> addresses the question of what fulfils the criterion of practical utility in a pharmaceutical invention. Brana's patent application was for antitumor compounds that exhibited better action and better action spectrum than known compounds of the same family (benzo(de)isoquinolines). This was rejected by the USPTO on the basis that it showed no practical utility. The examining board argued that

claims of 'treatment of diseases' and 'antitumor substances' could not stand the scrutiny of the utility standard set by *Brenner v Manson*.<sup>43</sup> The Court of Appeals rejected the argument on the ground that the patent application disclosed that the compounds had 'better action and better action spectrum as antitumor compounds'. This sort of comparison affirms that the claimed compounds are effective against lymphocytic leukaemia, the tumor model used in the experiments. These models also represented the specific disease that the compound would be effective against, and satisfied the utility requirement. 'In addition, the prior art discloses structurally similar compounds to those claimed by the applicant which have been proven *in vivo* to be effective as chemotherapeutic agents against various tumor models.' To the contention that the prior art has not been shown to be successful in clinical trials, but only in animal models, the Court replied, 'FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws... Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development'. The Board's decision was reversed and the patent was granted.

The US has come out with a three pronged test for utility which the applicant needs to satisfy for obtaining a patent on genetic inventions. The guidelines stated that not only must a 'credible utility' test be applied, a 'specific and substantial utility' must be provided in the disclosure. In 2001, the US Utility Examination Guidelines<sup>44</sup> were revised, and the utility standard was raised to limit the patenting of genes of unknown function. The guidelines required that the application must include a 'specific and substantial utility that is credible' and must have a 'well-established utility'.

According to the Guidelines, a utility is 'specific' when it is particular to the subject matter claimed. Now, a claim to a polynucleotide, which is disclosed as being useful as a 'gene probe' or a 'chromosome marker', would not be specific if the target is not disclosed. A 'substantial utility' is one that defines a 'real world' use. Credibility is established when a person skilled in the art acknowledges that the invention is 'currently available' for the use defined.<sup>45</sup>

In 2005, the law relating to 'utility' was clarified in the *In re Fisher* case.<sup>46</sup> The patent application by Dane K Fisher and Raghunath V Lalgudi is the most recent development in the long series of discussion between

the USPTO and the other biotechnology and pharmaceutical industry attempting to define the scope of DNA-related patent claims and the invention's utility. Dane K Fischer and Raghunath Lalgudi (collectively addressed as 'Fischer') inventors from Monsanto, had appealed the rejection of their patent application serial no. 09/619,643, (the '643 application), which was a USPTO Court of Appeals Federal decision before the Court of Appeals Federal Circuit. This patent ('643) had claimed patent for five purified nucleic acids that encodes protein and protein fragments in maize plant. These claimed nucleotides were referred to as ESTs. The ESTs disclosed in the '643 application were obtained from cDNA library LIB3115, which was generated from pooled maize leaf tissue at the time of anthesis from maize plants. The five ESTs sequences were designated as SEQ ID NO: 1 through SEQ ID NO: 5 in the patent specification and consisted of 429, 423, 365, 411, and 331 nucleotides, respectively. To satisfy the utility criteria for patentability, the following uses of the claimed ESTs were listed:

1. They serve as a molecular marker for mapping the entire maize genome, which consists of ten chromosomes that collectively encompass roughly 50,000 genes;
2. They measure the level of mRNA in a tissue sample via micro-array technology to provide information about gene expression;
3. They provide a source for primers for use in the polymerase chain reaction (PCR) process to enable rapid and inexpensive duplication of specific genes;
4. They identify the presence or absence of a polymorphism;
5. They can be used for isolating promoters via chromosome walking;
6. They control protein expression; and
7. They are used for locating genetic molecules of other plants and organisms.

The inventors were of the opinion that since the claimed ESTs served as a research tool it satisfied the utility requirements for the grant of a patent.

However, the USPTO Board of Appeals held that the disclosed uses were not specific to the claimed ESTs and could be applied to any EST. The claimed application was also rejected for lack of enablement, the reason being that one skilled in the art would not know how to use the claimed ESTs because the '643 application did not disclose a specific and substantial

utility. Thus the Federal Circuit (CAFC)<sup>46</sup> upheld the rejection of the USPTO Board of Appeals in September 2005.

Europe has also strengthened its industrial applicability standard with respect to genetic invention patents. Previously, European patent examiners and Courts applied this requirement liberally. Article 57 of the EPC explains that 'an invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture'. The EPC, and countries whose laws had been amended in compliance with the EPC, were in conflict with the EU Biotechnology Directive of 1998, which established a higher utility standard. The EPC was not created by the EU, and was not bound by the Directive, and yet the Administrative Council of the EPO incorporated it (the Directive) into the EPC in a new chapter- Biotechnological Inventions.

The Trilateral Project (USPTO, EPO, and JPO) has studied in detail the patentability of ESTs and DNA fragments.<sup>47</sup> The conclusions that were drawn are:

1. A mere DNA fragment without indication of a function or specific asserted utility is not a patentable invention.
2. A DNA fragment, of which specific utility, e.g. use as a probe to diagnose a specific disease, is disclosed, is a patentable invention as long as there [are] no other reasons for rejection.
3. A DNA fragment showing no unexpected effect, obtained by conventional method, which is assumed to be part of a certain structural gene based on its high homology with a known DNA encoding protein with a known function, is not a patentable invention (EPO, JPO). The above-mentioned DNA fragment is unpatentable if the specification fails to indicate an asserted utility (USPTO).
4. The mere fact that DNA fragments are derived from the same source is not sufficient to meet the requirement for unity of invention.

Additionally, at the trilateral meeting in June 2000, it was concluded that

1. All nucleic acid molecule-related inventions, including full-length cDNAs and SNPs, without indication of function or specific, substantial and credible utility, do not satisfy industrial applicability, enablement or written description requirements.



2. Isolated and purified nucleic acid molecule-related inventions, including full-length cDNAs and SNPs, of which function or specific, substantial and credible utility is disclosed, which satisfy industrial applicability, enablement, definiteness and written description requirements would be patentable as long as there is no prior art (novelty and inventive step) or other reasons for rejection.

#### Sufficiency of Disclosure

Another aspect, which has to be considered for patentability of gene/DNA sequences, is the sufficiency of the specification of such inventions. In many cases the disclosures are unable to describe the inventions sufficiently well so as to achieve the results as claimed by it. The effect of making a broad claim has frequently led to invalidating the patent for lack of subject matter. However, in the case of biotechnological inventions a new scenario arises where a given result may be obtained by different means and the various means have nothing in them, which can relate to the subject matter disclosed in a specification. This is a type of insufficiency, which is called the *Biogen* insufficiency. The term was coined in the House of Lords decision in *Biogen v Medeva*.<sup>48</sup> The patent claimed a recombinant DNA molecule characterized by the sequence of the antigens, namely core and surface antigens. The patent was held invalid in the House of Lords which consented that even though the patent enabled the production of both antigens by the single method described, the claims were for every way of achieving the stated result, namely the production of antigens.

#### Ordre Public and Morality

In addition to the criteria of novelty, non-obviousness and utility, in India and in the EU, the subject matter for the patent must not be contrary to *ordre public*<sup>49</sup> and morality.

TRIPS Article 27.2 states that members may exclude from patentability such inventions as is 'necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment'. This has been incorporated in Section 3(b) of the Indian Patents Act.<sup>50</sup>

A suitable example for this exclusion in Europe is the *Howard Florey Institute/Relaxin Case* (V008/94).<sup>51</sup> Here, the claims were toward a method for synthesis of peptides with relaxin activity, which

included synthesis of relaxin and certain analogues of relaxin. Relaxin is an ovarian hormone that softens and lengthens the inter-pubic ligaments during pregnancy. It also dilates the cervix and inhibits contractions of the uterus. The patent granted was for a process of producing relaxin from a cDNA fragment and a product such as the gene sequences coding for the relaxin molecule.

The patent was opposed by the *Fraktion der Grünen im Europäischen Parlament* (the Green Party of the European Parliament) and Paul Lannoye on the grounds that the subject matter of the patent was not patentable due to the lack of novelty and an inventive step, and that it offends the *ordre public* and morality.<sup>52</sup> The Opposition Division of the EPO did not agree with the oppositions. The claimed DNA fragments encoding relaxin and its precursors were cDNAs and these cDNAs do not occur in the human body. Thus the sequences were considered novel. Prior to the cDNA encoding human H2-relaxin isolated by the Howard Florey Institute, the existence of this form of relaxin was unknown. 'It is established patent practice to recognize novelty for a natural substance which has been isolated for the first time and which had no previously recognized existence'. Since the isolated gene was novel, the Institute was not preparing a known substance, but was using entirely new methods to isolate the gene and produce the relaxin molecule. Thus this was considered as an inventive step.

The opposition to the patent argued about the *ordre public* and morality clause as follows:

(a) The patent teaches that in order to repeat the invention, tissue is to be taken from a pregnant woman. The isolation of the DNA relaxin gene from tissue taken from a pregnant woman is immoral, in that it constitutes an offence against human dignity to make use of a particular female condition (pregnancy) for a technical process oriented towards profit.

(b) The patenting of human genes such as that encoding H2- relaxin amounts to a form of modern slavery since it involves the dismemberment of women and their piecemeal sale to commercial enterprises throughout the world. This infringes the human right to self-determination.

(c) The patenting of human genes means that human life is being patented. This is intrinsically immoral.'

'A fair test to apply is to consider whether it is probable that the public in general would regard the

invention so abhorrent that the grant of patent rights would be inconceivable. If it is clear that this is the case, objection should be raised under Article 53(a); otherwise not'. The Opposition Division held that the patent did not conflict with Article 53(a) and rejected the opposition of the patent.

The BRCA case also highlights the importance of acceptability of gene patents to the general public. The BRCA gene patents have been subject to great scrutiny and opposition in the past few years. Mutations in the BRCA1 and BRCA2 genes are considered responsible to cause a majority of the cases of inherited breast cancer. Hereditary breast cancer accounts for five to ten percent of all breast cancers.<sup>53</sup> Women carrying a germ-line mutation of BRCA1, for instance, have an 85% risk of developing breast cancer in their lifetimes, when the general population's risk stands are around 12%. Risks attached to BRCA2 mutations are comparable.

By 2003, the EPO had granted four patents to Myriad Genetics, covering both the BRCA1 and BRCA2 genes. Thus Myriad got an exclusive monopoly over diagnostic testing of BRCA1 and BRCA 2 in almost all the European countries, since the first patent EP0699754 covered methods of diagnosis, the second, EP0705903, covered specific mutations of the BRCA1 gene and the third, EP0705902 covered the gene itself, the protein and possible diagnostic kits. The fourth patent, EP0785216 on the BRCA2 gene, covered not only the sequence of the gene but also use of this information for diagnosis, risk prediction, screening or therapy.

Since the BRCA genes were under exclusive patent protection in Europe, no European nation could undertake the diagnostic testing, and had to send the samples to the Myriad's laboratory in Utah. This process cost more than three times the amount it would have if testing were carried out in Europe. Moreover, this enabled Myriad to build the only BRCA databank, giving it another monopoly, this time over research materials relating to all genes responsible for breast cancer susceptibility. There was also opposition to the fact that in the first patent filed by Myriad (in the US) the gene sequences were incorrect.

The first Myriad BRCA patent (EP 699754) was revoked in May 2004, after opposition procedures for two days. The revocation was based on a lack of clarity, insufficient disclosure and lack of inventive step. The Opposition Decisions on the second and

third patents, EP 705903 and EP 705902, held that the claims towards diagnostic methods, which included claims to the gene as a chemical molecule, claims to the protein, therapeutic applications, diagnostic kits and transgenic animals were invalid. This left Myriad with a patent for the nucleic acid probe and the vectors containing the BRCA1 gene (EP 705902), and a patent to a single mutation in the BRCA1 gene (EP 705903). Opposition proceedings were heard against EP0785216 in June 2005, and resulted in the claims being amended to cover only the use of the BRCA2 gene for diagnostic testing of Ashkenazi Jewish women.<sup>54</sup> As a result, the exclusive monopoly of Myriad Genetics over the BRCA genes and their use in research and diagnostics was effectively overturned in Europe.

In summary, once it is established that the claim in a patent is novel, non-obvious and useful, genes and gene products can be patented. With regard to utility a higher utility standard is applied both in the US and Europe. In the US, a three-pronged test has to be satisfied. Further enablement and written description is a further requirement in the case of genetic inventions. Protection of genetic inventions will foster development and will augur well for the society because it is the society which will ultimately reap the benefits of genetic inventions.

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- 2 [www.uoguelph.ca/~hlee/426chap1.htm](http://www.uoguelph.ca/~hlee/426chap1.htm).
- 3 First amendment - Indian Patents (Amendment) Act, 1999 (No. 17 of 1999 (26 March 1999).
- 4 Second amendment - Indian Patents (Amendment) Act, 2002 (No. 38 of 2002) (25 June 2002).
- 5 Third amendment - Indian Patents (Amendment) Act, 2005 (No. 15 of 2005) (4 April 2005).
- 6 Section 5 (now omitted) read as follows:  
 'Inventions where only methods or processes of manufacture patentable  
 1. In the case of inventions-  
 (a) claiming substances intended for use, or capable of being used, as food or as medicine or drug, or  
 (b) relating to substances prepared or produced by chemical processes (including alloys, optical glass, semi-conductors and inter-metallic compounds),  
 no patent shall be granted in respect of claims for the substances themselves, but claims for the methods or processes of manufacture shall be patentable.

2. Notwithstanding anything contained in sub-section (1), a claim for patent of an invention for a substance itself intended for use, or capable of being used, as medicine or drug, except the medicine or drug specified under sub-clause (v) of clause (1) of sub-section (1) of section 2, may be made and shall be dealt, without prejudice to the other provisions of this Act, in the manner provided in Chapter IVA.
- 7 27 (1) ' Subject to the provisions of paragraphs 2 and 3, patents shall be available for all inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application... Patents shall be available and patent rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced'.
- 8 Lehninger-Principles of Biochemistry, Fourth edition, (Nelson & Cox), 2005.
- 9 Section 3, Indian Patents Act, 1970.
- 10 Section 3(b) reads as follows 'an invention, the primary and intended use or commercial exploitation of which would be contrary to public order or morality or which causes serious prejudice to human, animal or plant life or health or to the environment.'... are not inventions.
- 11 502 US 856.
- 12 Howard Florey/Relaxin 1995 OJEPO 388.
- 13 Biotechnology Directive (98/44/EC).
- 14 Section 3 (c) reads as 'the mere discovery of a scientific principle or the formulation of an abstract theory or discovery of any living thing or non-living substances occurring in nature' are not inventions.
- 15 Article 52 (2) of EPC which reads as 'the following in particular shall not be regarded as inventions within the meaning of paragraph 1: (a) discoveries, scientific theories and mathematical methods.
- 16 Guidelines, C:IV 2.3, Revision of February 2001.
- 17 *Funk Bros Seed Co v Kalo Inoculant Co*, 333 US 127 (1948). The US Supreme Court stated, Patents cannot issue for the discovery of phenomena of nature, ' and 'these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none.' One can argue that genes, like the bacteria in *Funk Brothers*, are a 'discovery of the phenomena of nature,' and therefore genes should not be patentable.
- 18 447US 303.
- 19 35 USC101 '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 there for, subject to the conditions and requirements of this title'.
- 20 Federal Register/ vol 66, no. 4/ Friday, January 5, 2001/ Notices.
- 21 427 F 2d at 1401-02.
- 22 35 USC102 (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.
- 23 35 USC 103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in Section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.
- 24 *In re O'Farrell*, 853 F 2d 894, 903-04, 7 USPQ 2d (BNA) 1673, 1681 (Fed Cir 1988).
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- 34 *In re Deuel*, 51 F 3d 1552, 1559 (Fed Cir 1995).
- 35 *In re Deuel*, 51 F 3d 1552, 1558 (Fed Cir 1995).
- 36 *In re Deuel*, 51 F 3d 1552, 1557 (Fed Cir 1995).
- 37 *In re Deuel*, 51 F 3d 1552, 1158 (Fed Cir 1995).
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- 40 <http://www.news.uiuc.edu/scitips/00/11head.html>.
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- 44 USPTO, Utility Examination Guidelines. 60 Fed Reg 36.
- 45 The fate of gene patents under the new Utility guidelines, *Duke Law & Technology Review*, 8 (2001).
- 46 *In re Dane K Fisher and Lalgudi V Raghunath*, 04-1465.
- 47 Trilateral project B3b. Comparative Study on Biotechnology Patent Practices Theme: Patentability of DNA Fragments
- 48 *Biogen v Medeva* [1997] RPC1.
- 49 *Ordre Public* best translates as Public Policy in English. It is the body of fundamental principles that underpin the operation of legal systems in each state. In Indian Patent Law, the clause says '...an invention the primary or intended use or commercial exploitation of which could be contrary to public order or morality...'

- 50 Section 3 (b) reads as follows 'an invention, the primary and intended use or commercial exploitation of which would be contrary to public order or morality or which causes serious prejudice to human, animal or plant life or health or to the environment.' ... are not inventions.
- 51 <http://legal.european-patent-office.org/dg3/biblio/v940008ep1.htm> or 1995 OJEPO 545.
- 52 Article 53 of the EPC *Exceptions to patentability* European patents shall not be granted in respect of: 'inventions the publication or exploitation of which would be contrary to *ordre public* or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States'.
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