Question Q 150

Patentability Requirements and Scope of Protection of Expressed Sequence Tags (ESTs), Single Nucleotide Polymorphisms (SNPs) and Entire Genomes

Introduction

This question considers issues surrounding certain inventions in the field of biotechnology. A short description of the technology is set out in the Working Guidelines (Yearbook 1999/1). To recap, the entire DNA sequence of an organism is known as the genome. A copy of the genome is found in most cells in the body. A large proportion of the DNA in the mammalian genome does not appear to encode any known protein. Within the genome are genes - sections which encode proteins. The DNA code of genes is transcribed to form mRNAs, which are in time translated to produce proteins.

ESTs are short random fragments of DNA. They are isolated from mixed mRNAs and converted back to cDNAs. Because each EST is related to an mRNA, it must represent the part of a gene which encodes a protein. Using known techniques the location of the EST on the genome can be determined.

SNPs are sites in the genome in which there is variation among the population of one base in the sequence. Many SNPs are in the regulatory regions, in promoters, rather than in coding regions of the genome.

ESTs and SNPs are important because of their potential use in understanding genetics and diseases. If a certain population with a certain condition is found to have the same SNP, that may be significant. The production of a particular protein associated with a condition may be investigated through an EST.

Genomes may be discovered through research into diseases. For example researchers have isolated and patented the genome of Hepatitis C.

Patents for such inventions can raise legal, technical and moral questions. Legal questions concerned include scope of protection for such inventions.

The Reporter General received 24 Reports from the following Groups: Argentina, Australia, Austria, Belgium, Brazil, Denmark, Finland, France, Germany, Great Britain, Hungary, Israel, Italy, Japan, Mexico, The Netherlands, Republic of Korea, Romania, South Africa, Spain, Sweden, Switzerland, the United States of America and Uruguay.

The reports give an excellent overview of the law in the reporting countries.

A number of Groups noted by way of introduction that even where there had been litigation in national courts about bio-technology patents, there had been few disputes about ESTs or SNPs. The Mexican Group noted the importance of the topic for countries having a great bio-diversity, which tend to be in the developing, rather than the developed, world. The question of biodiversity will be studied further during the Melbourne Congress in 2001.

1(a) Are ESTs, SNPs and genomes inventions the patenting of which is contrary to "ordre public" or morality (TRIPS, Article 27.2)?

The Groups were unanimous that patenting ESTs and SNPs did not raise "ordre public" problems. But there was a range of views so far as genomes were concerned particularly on questions of patenting the human genome. The US Group noted a particular concern about chimeras involving the human genome. There is a widely publicised (but unpublished) US patent application claiming part-human chimeras - animals which are part-human, part-other (The USPTO press release is at **http://www.uspto.gov/web/offices/com/speeches/98-06.htm**.)

The US Group noted:

> "It has been indicated that the USPTO would regard patent claims which "embrace a human" as violative of the Thirteenth Amendment to the U.S. Constitution, which prohibits the slavery. ...A claim to a human genome, i.e., the entire DNA of an individual - even if novel and unobvious - could, according to this USPTO position, violate the Constitutional prohibition and thus be unpatentable. Where, as in the case of chimeras, the claimed invention comprises more than human genetic material, the USPTO's position is less clear."

The Danish Group considered that the patenting of the human genome would be contrary to morality, as being in contradiction with the declaration of human rights under Danish constitution. However, the Danish Group thought that there should be no problem with isolated sequences of Genomic DNA, with the caveat that if human generic DNAs claimed using the term "comprising" then there would be a problem.

The Korean Group was against the patenting of ESTs as it could "hinder the filing of an application for a complete invention which elucidates the full sequences and functions of genes." This was contrary to morality.

The Swiss Group thought that the monopolisation of the human genome for the purpose of personal profit could be regarded as contrary to ordre public or morality. Patenting the human genome would be contrary to the Swiss constitutional guarantee of human dignity.

The Israeli Group noted that:

> "It is not coincidental that pro-active groups that support patenting of human genes, are organisations of individuals and their families of sufferers from genetic disorders".

The Italian Group suggested that the matter might be considered one of private property law, and that material derived from one individual should not be taken in via violation of such laws. Where problems arose, compulsory licensing could help.

1(b) Are Patent Offices the correct places to determine these questions and do they have sufficient resources to make such decisions?

There was a spread of views on the question of the role of Patent Offices. The majority believed that Patent Offices were not the correct place to decide policy questions, even though they might have the power and appropriate precedents to enable them to do so to decide such questions. The Danish, Dutch and Korean Groups believed that Patent Offices were the correct place for such decisions to be taken. The Dutch Group thought the EPO had the ability to make such decisions.

The German Group noted that the transfer of the issue outside patent offices would slow down the granting procedure; that would be unfair. Such questions are for the legislature, executive or courts. A number of groups commented on the benefits that might flow from Patent Offices being allowed to obtain expert advice (Denmark, Italy, Romania, Spain and South Africa (suggesting the Court of Commissioner of Patents)).

Groups were generally agreed that there were insufficient resources in Patent Offices to make such decisions.

The Finnish Group noted that:

> "... it should be emphasised that a granted patent is not a permission to use the patented invention. Such permission is against the result of other legal provisions ..."

2 *What level of utility should be required of patents for ESTs, SNPs and Genomic DNA?*

The Groups agreed that the same level of utility (or industrial applicability) should be required of ESTs, SNPs and genomes that is required of other areas of technology. But Groups did differ in the way they saw this applying to ESTs. The view of the Argentinean, Belgian, Danish, German, Japanese and US Groups was that an EST should have some utility beyond being a mere probe. The German Group noted that ESTs might be useful as diagnostic tools.

According to US law it is not sufficient for patentability that a compound is useful for further research. Patentability requires the disclosure of "a practical utility - not merely use of further research". Accordingly, it may be that claims to partial DNA sequences which have only disclosed utility for further research - gene mapping or probing to isolate a full length sequence whose function is unknown - are unpatentable. This view was shared, amongst others, by Denmark, Hungary, Israel, Romania and South Africa.

The British Group pointed to Article 5(3) of the EC Directive on the Legal Protection of Biotechnological Inventions, which provides:

> "The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application".

The EPO has observed, discussing this rule that:

> "Thus where such sequences are the subject matter an invention, it is necessary to indicate in particular what function is performed by the sequence and the protein built from it".

The British Group observed the view that the EPO view was a gloss on Recitals 23 and 24 of the directive which "goes too far and is not mandated by the directive".

The Australian Group noted:

> "It is clear that ESTs and SNPs should always be useful as probes. This use should be sufficient to satisfy the requirement that the invention is useful. If, however no information is provided as to what specific use as probes ESTs or SNPs have (which would require some information as to the gene which the ESTs or SNPs are derived), then the ESTs or SNPs are unlikely to be patentable on the grounds of obviousness ...".

The French Group noted that the French version of Article 5(3) of the Directive states that:

> "The industrial application of a sequence or a partial sequence of a gene must be disclosed *in concrete terms* in the patent application". (Added italics)

The French Group added that Recital 23 of the Directive provides that a simple sequence of DNA without any indication of a function did not contain any technical teaching and thus should not be patentable. This provision aims at excluding from patentability DNA sequences that do not contain any technical teaching but that would be capable of industrial applicability because could be produced in the industry. The French Group concluded that the technical teaching of a DNA sequence is thus given by its function.

3. Is an EST or a SNP an "invention" at all?

There was a range of views on this question. The majority believed that ESTs and SNPs are "inventions". In particular a number of groups which follow the European Patent Convention noted that "presentations of information" are not patentable inventions, but the British Group noted that although an EST or SNP might therefore be considered to be "information", it had a practical application and was therefore not excluded from patentability. In the US, inventions and discoveries are patentable so long as "a composition of matter" can be found. That covers ESTs and SNPs. The South African and Swedish Groups pointed out that prior existing micro-organisms are patentable, so long as they satisfy the other criteria of patentability. By analogy, isolated genes and sequences should be patentable too. The Danish and Spanish Groups thought that the mere identification of fragments existing in nature were not patentable. The Australian Group thought the question turned on the disclosure given.

The Korean Group thought ESTs and SNPs "are not inventions because they are mere pieces of information".

4(a) Do ESTs, SNPs or genomes form part of the state of the art in relation to full length gene sequences?

4(b) If it is possible to patent an EST or SNP, should a later, longer gene sequence including that EST or SNP nevertheless be regarded as novel?

Groups agreed that ESTs, SNPs and genomes should be treated like other inventions and should form part of the state of the art in the same way. Accordingly, it should be possible to patent a longer, gene over an earlier described EST or SNP if the earlier description did not provide all the elements of the later invention. However, as the French Group noted, characterised and reproducible ESTs, SNPs and genomes, might prevent a later patent application the object of which would be a sequence of nucleic acid "comprising" these SNPs, ESTs or stemming from these genomes. Accordingly a later foreign gene sequence including a known EST or SNP should be regarded as novel. The German Group noted that disclosure of one chemical should not affect the novelty of a patent for another.

The Italian Group noted that where a Genome was known, the later discovery of an EST might give rise to a patentable selection invention.

The Japanese Group noted that an EST might make a longer gene obvious.

The Spanish Group noted that a new activity or utility would be needed for a longer later gene to be patentable.

The Danish Group noted that novelty should be evaluated by the same objective standards worldwide. Standards of "local novelty" or "novelty in respect of written disclosures" should be repeated since they could be used to abuse the patent system.

5(a) What standard of obviousness should apply to inventions concerning ESTs, SNPs and genomes?

There was a wide measure of agreement that the same standards of obviousness should apply to inventions concerning ESTs, SNPs and genomes as apply to other inventions. Having regard to the EPO's case law, the French Group stressed the importance of such notions as the "skilled person in the art", the "would-could approach" and the notion of chances of success. The Israeli, Italian and British Groups pointed to the link between obviousness and utility, such as illustrated by the European Patent Office in its decision in Agrevo/Triazole herbicides. In that case the EPO Technical Board of Appeal found that it was obvious to make a chemical with no known utility, because where the object of an invention was to make new chemicals, all chemicals were equally obvious.

The US Group notes that "the fact the methods for generating and sequencing ESTs and SNPs are known is irrelevant to the patentability of the specific DNA molecules".

The Korean Group was concerned about patenting the human genome, noting that it might be obvious to disclose ESTs and SNPs.

The Swiss Group suggested that the inventive step will lie in surprising technical qualities and useful applications.

The Italian Group noted the danger of allowing the introduction of inventive features following the date of application. This would allow early speculative applications.

The most significant problem appears to be a lack of sufficient information.

5(b) What particular difficulties does courts and patent examiners face in assessing inventive step?

A number of groups suggested that Patent Offices would have difficulty obtaining sufficient information to check the inventiveness of such inventions. Improvements thus appear desirable the US Group suggested that high speed computers and databases be available. The South African Group called for the availability of experts opinions. The Argentinean Group suggested international corporation between Patent Offices.

6. What should be the sufficiency requirements for patents for ESTs, SNPs and genomes DNA?

There was broad agreement that the same sufficiency criteria should apply to these inventions as to other inventions. The British, French, South African and US Groups noted the issues raised by unduly broad claiming. The British, French and Korean Groups noted that the claimed breadth should correspond to the technical contribution to the art. A number of groups noted that claims to ESTs of little function other than probes should be insufficient where "comprising" language was used to claim a full length gene. The US Group illustrated such a claim as follows:

> "A nucleic acid to which a DNA having the sequence of SEQ ID NO. 1 will hybridise under stringent conditions."

The US Group noted that claims of this scope present difficult enablement issues, because they probably would encompass a longer DNA molecule, including a full-length gene whose structure and function were unknown at the time of filing.

The Hungarian Group suggested that there should be strict rules for sufficiency including the listing of a full sequence "without deviations".

7. Are there, or should there be special provisions for the written description or claims (e.g. considering unity of invention) of ESTs, SNPs and genomes?

There was agreement that there are not and should not be special provisions for the written description or claims of inventions covering ESTs, SNPs and genomes. The French and Belgian Groups mentioned that presentation standards have already been fixed by WIPO. The US Group noted the US requirement that the application must describe an invention "in sufficient detail that a person skilled in the art "can clearly conclude that 'the inventor invented the claimed invention [as of the filing date]' ".

The Australian, German, Israeli and South African Groups called for the possibility of filing applications electronically to avoid the increase in printing and handling costs. The South

African Group noted that applications greater than 20,000 pages might soon appear. The Brazilian Group called for the possibility of filing on diskette.

The Danish Group believes that a general harmonisation in deciding unity of invention is required. The group noted that the USPTO applies "different standards depending on whether an application is a PCT or a national application".

On the question of unity of invention the South African Group noted:

> "In Europe, applicants for ESTs are trying to avoid filing separate applications for each DNA sequence by using Bioinformatics to establish a common "functional domain" in the ESTs claimed, thereby providing the necessary technical relationship between the ESTs to overcome any objections on the grounds of lack of unity of inventions. However, the allocation of some common function is not always precise in some cases, the sequences being described very generally as "receptors" or "signalling molecules". In reality the actual biological function of these molecules is likely to be quite different and lack of unity of invention objections could still arise where the state of the art is different for individual molecules within the generic group".

The Italian Group noted that:

> "The principles codified in Article 82 and Rule 30 of the EPC are applicable for the unity of invention and should rely on structural homology, functional and utility relationships among a plurality of the inventions claimed in the same patent application, provided the common features are clearly expressed or maybe readily determined from the description".

The Hungarian Group suggested:

> "While unity requirement might be fulfilled by disclosing identical utility of more ESTs or SNPs in the same application, it is suggested that each claim shall relate to one and fully defined sequence only".

The French Group noted that a compromise could be reached where the unity of invention criteria could not be fulfilled, for example by restricting the number of ESTs by the claims.

The Dutch Group emphasised by specifications should disclose which elements of a SNP, EST or genome correlated with the inventive step.

8(a) Should patent claims for ESTs, SNPs and genomes afford the same protection as other patent claims?

The general view was that patents for ESTs, SNPs and genomes should afford exactly the same protection as for other patent claims. The Japanese and Israeli Groups noted under this heading (as had other groups in other sections) that the scope of protection should be related to the contribution to the art. Referring to Articles 8 and 9 of the Directive which deal with the potential extension of protection to derivative products, the French Group noted that derivative products will be

protected by extension if they contain the same properties or fulfil the same function. The British Group pointed out:

> "Articles 8, 9 and 10 of the Biotechnology Directive have provisions as to scope which ... we consider to be essentially declaratory of existing law. Early drafts of the Biotechnology Directive supplemented existing provisions of patent laws as to "experimental use relating to the subject matter of the invention" ... but the final version has nothing to say on the subject.

The Korean Group thought that protection for ESTs should be limited to known use.

The Belgian Group also noted the availability of the experimental use exemption in Europe as did the US Group for the US.

The US and Israeli Groups noted the problems that might arise where a patented EST is used for isolating a full length gene that is subsequently used to develop a pharmaceutical product. A question arises whether the holder of the EST patent is entitled to some form of royalty based on the sale of the pharmaceutical product. This may present problems in the future.

The Italian Group noted the wide use of EST as research tools did not justify any departure from existing rules.

8(b) *If the answer to (a) is "no" could there be restrictions on the scope of protection of such patents, e.g:*

(i) restriction to the known use of the gene (or fragment);

(ii) compulsory licensing by the patentee so as to make research tools available for further inventions.

The Groups (with the exception of Israel) did not call for the availability of compulsory licences in this field.

The US Group noted that compulsory licensing "has long been disfavoured in the United States". US courts do have the authority to consider the public interest in deciding whether to issue an injunction against patent infringement; however, an injunction usually will issue once there is a find that the asserted patent is infringed and has not been proven to be invalid or unenforceable. In contrast, the Israeli Group called for the availability of compulsory licensing for research tools.

The Danish Group argued against compulsory licensing:

> "... suggestions are providing general "licences of rights" available for "research tool" patents are based on a misunderstanding of the patent system. A patent is the result of an investment and human creativity, similarly to the production of a new NMR spectroscope, but nobody requires a NMR producer to make machines available to customers who are not willing to pay the price. At the same time, the present patent system allows free use by third parties of patented subject matter for research purposes. Thus the present patent system seems to be sufficient to secure third party's rights to

search for further information in connection with EST, SNP and genomic DNA without being limited by patents".

The Finnish Group, under this heading, called for the scope of protection to be limited to the scope of disclosure. The Finnish Group suggested that AIPPI investigate use of "research tools". It appears, however, that this issue is not specific to this technical field and therefore no specific exception should be developed.

Conclusions

The views of the majority of the groups answering the questions raised in the working guidelines are as follows:

1. Patenting ESTs, SNPs and simple genomes does not raise "ordre public" problems but patenting the human genome may raise problems of morality. Patent Offices are not the correct place to determine such questions; they do not have sufficient resources to make such decisions.

2. The same level of utility (or industrial applicability) should be requested of ESTs, SNPs and genomes as is required of other areas of technology. However, the working Committee should consider the AIPPI position on the level of utility which should be required for ESTs and SNPs, as a significant minority of groups consider that disclosure of utility should go beyond the mere general indication of a utility as probe for further research.

3. ESTs and SNPs are "inventions".

4. ESTs, SNPs and genomes should be treated like other inventions and form part of the sate of the art in the same way.

5. The same standards of obviousness should apply to these inventions as to other inventions. AIPPI also wishes Patent Offices to develop and harmonize appropriate tools for examining the novelty and inventive step of inventions related to ESTs, SNPs and genomes.

6. The same sufficiency requirements should apply to these inventions as to other inventions.

7. There are not and should not be special provisions for the written description or claims of inventors covering ESTs, SNPs and genomes. As shown by several group reports, AIPPI also wishes that harmonized standards be established on an international level for evaluating unity of invention during the examination of patent applications concerning ESTs, SNPs and genomes.

8. Patents for ESTs, SNPs and genomes should afford exactly the same protection as for other patent claims. There is no need for special provisions relating to experimental use, research tools or compulsory licensing in this technical field.