

POLICY

Patenting and licensing in genetic testing: ethical, legal and social issues

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Introduction

The rise of patents on human genes during 1990s

The historical purpose of the patent institution is to promote research and innovation and to allow the return of new beneficial results returned to serve society. The price for this is a time-limited exclusivity granted to the inventor who can exclude others from using the invention.

The institution of a patent is very old, but its emergence in the field of genetics has confused many. The flow of patents on human genes has raised practical and ethical concerns, particularly in Europe. A large part of public opinion is against the principle of the patentability of life and, by inclusion, against the patentability of human genes. The research community is concerned with the foreseeable limitations of their research projects in the field. The health care professionals and payers are concerned with the anticipated impact of the patents on the cost of tests. The industry, especially the small and medium-sized companies, and the patent attorneys are concerned with the difficulties they may have to face because of multiple licences necessary to develop a new diagnostic kit or a new drug.

According to a recent estimate, patents have been granted or patent applications have been filed for nearly 20% of human genes.¹ For instance, major genes for

monogenic disorders (eg Huntington's disease, Cystic fibrosis) and some common predisposition genes (eg breast cancer BRCA1 and BRCA2) have already been patented.^{2,3} However, after the publication of the human genome in 2001, there was a clear decrease in patent filings, and gradually the bar on patentability has also been elevated.⁴ In particular, the European and Japanese patent examiners have had a more stringent approach compared to that of the US Patent and Trademark Office (USPTO).

Many international and national organisations have addressed the issue of patenting DNA, and while many of them basically acknowledge beneficial impacts of patents on public interest, they demand clearer guidelines^{2,5} or a more cautious approach.⁶ In particular, access to diagnostic tests has raised specific concern due to some licensing practices that have limited or hindered the access to them.⁷

The Nuffield Council (2002)⁵ has identified four uses on which DNA sequence patents have been concentrated:

- (1) Diagnostic tests: Inventiveness criterion needs stringent application. Possibility of 'use patents',
- (2) Research tools: Strict application of utility criterion. Patenting should be discouraged,
- (3) Gene therapy: The identification of a disease-specific gene should not be granted a product patent, but rather encourage the invention of safe and effective methods of gene delivery, and
- (4) Therapeutic proteins: Not the DNA sequence as such, but the protein described.

Several articles have suggested that patents block research and development, as well as hinder patients'

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access to recently available diagnostic tests.^{8,9} For instance, a survey by Cho *et al*⁸ found that patents and licences have had a significant negative effect on the ability of clinical laboratories to develop and provide genetic tests, and to perform research.

On the contrary, it has been argued that if inventors were not rewarded by their innovations, some important developmental initiatives with a high risk for failure might be hampered^{10,11} and adversely affect research in certain fields. Industry has significant impact on scientific innovation in the field of biomedical advancement. Developing research tools, for instance, takes time and effort, but once made publicly available, many biotech companies can access them and further their own research. It is said that many of the problems arise out of overly restrictive or monopolistic licensing policies of the patent holder rather than the patent system itself.

Policy-making in the field of patents is difficult due to the many stakeholders with varying interests. The public discussion on patenting human genes has been described as 'mixing oil and water',¹² because the professionals' and laypeople's understanding and views of the issue are often distant from each other. More so, it is not only laypeople's and professionals' views that diverge, but also that among professionals there are huge contradictions. In addition, it has been suggested that policy-makers have responded more to the high-profile media controversies than to systematic data about the problems and situation in reality.⁷ A European wide IPR-policy should create a balance between competitiveness and the European moral values to keep benefits of the inventions in Europe. However, as the patenting practice of the United States (US) also has an influence on European industrial practices, it is evident that the European framework should not create a competitive disadvantage. In this complicated environment, sound policy-making is extremely challenging.

The European Society of Human Genetics (ESHG) decided that it was time to establish a dialogue between all stakeholders, to review the facts and to identify ways to improve the current patent system applied to the genetic testing field, to better serve the public while respecting current legislations.

The current paper reports on the results of this process which has been handled by the Public and Professional Policy Committee (PPPC) and the Patenting and Licensing Committee (PLC) of the ESHG.

Definition of a patent

A patent may be defined as 'a grant by the state of exclusive rights for a limited time in respect of a new and useful invention, usually limited to the territory of the state granting the patent'.¹³ Therefore patent protection outside a country requires an individual patent in each country, facilitated by centralised international filing procedures.

A patent right to an invention does not give a right to use the invention, but only the right to prevent others from using it commercially (see Patents). Thus, the use of the invention has to comply with other relevant regulations.

A genetic substance that can be reproduced by using artificial means, as with the isolation and cloning of a gene, is regarded as an artefact, a man-made invention, and is, therefore, eligible for patenting on the condition that the substance, its function, or a method to produce it is an invention, is novel, has a specific disclosed function, is not obvious with respect to current knowledge, and can be applied industrially.

Within its recommendation on the licensing of genetic inventions, the OECD defined a genetic invention to include nucleic acids, nucleotide sequences and their expression products; transformed cell lines; vectors; as well as methods, technologies and materials for making, using or analysing such nucleic acids, nucleotide sequences, cell lines or vectors.¹⁴

Patent claims can be subject to different kinds of DNA sequences. These include full-length DNA sequences, partial sequences, expressed sequence tags (ESTs), and single nucleotide polymorphisms (SNPs). Patent claims pertaining partial DNA sequences, ESTs and SNPs have raised particular concern.^{5,15}

The basic patentability criteria are (i) an invention, (ii) novelty, (iii) inventive step, and (iv) industrial applicability, and these criteria are required in the European Patent Convention (EPC) and subsequently in national patent laws. There have been further specifications in the EU Biotechnology Directive 98/44. Despite the internationalisation of patent filings and implementation of international patent instruments into the national laws, the practices of the European Patent Office (EPO) and national patent offices vary and national laws have their own particularities, which makes the international patent framework unclear and unpredictable at times.

Once a patent is granted, it may be used to limit the commercial and professional use by others: as to be able to use the patented method, a prospective user needs a licence. An example of an invention globally used by way of a licence is the PCR technology covered by patents owned by F Hoffmann-La Roche Ltd. Rapid advancements of biotechnology are said to be possible because of collaboration and co-operative licensing between several actors in the field.¹⁰

Concerns relating to the genetic patents

The most current concerns about genetic patents relate to their consequences (upstream patents *vs* downstream ones), some patent-holders' abusive use of their monopoly position, patent-thickets (ie overlapping sets of patent rights with different ownership, requiring several licences), overly broad patent claims; and blocking patents due to defensive IPR policies of the companies. Many companies

file patent applications for defensive purposes (ie to ensure freedom to operate), but seldom pursue them. There is often an assumption that all applications filed will be granted, or that they are even already 'patents' before this. These problems are viewed as hindering further research and development, increasing the costs and/or to preventing access to new diagnostic tools in clinical practice. In the United States, one survey reported that 25% of the interviewed genetic clinics had stopped performing a clinical genetic test because of a previously existing patent or licence.⁸ Other reports, however, have not yet found significant burdens for biomedical researchers, though it is anticipated the situation is changing in this direction.³

Most factors, other than genes, affecting the function of the human DNA are still not well understood. Recent knowledge suggests that non-coding DNA ('junk-DNA') is much more significant than previously assumed. For example, as epigenetic regulation affects gene expression, it has been claimed that modern genetic research should shift its focus to epigenetic factors to understand the genetic framework.¹⁶ Patents over non-coding biological materials further complicate the situation simply because patent claims wrongly assume that knowledge of their existence equals knowledge of how to apply this knowledge in medical and scientific research.

Therefore, it is essential for future research to ensure that existing gene patents do not block the possibility of studying factors that underlie or are associated with the functioning of a certain gene or its interaction with other factors, such as the environment.

It is anticipated that new areas of patenting might include diagnostic or prognostic tests based on gene expression profiling or SNPs, and therapeutics based on RNA interference. Such patent filings might reopen concerns on the anticommons effect and patent thickets.^{4,17} Biochip development will enable rapid detection of hundreds of genetic mutations, but practising this might also violate hundreds of patents.

These and other prospective new uses of a gene sequence that were not anticipated at the time of a patent application might give undeserving benefit to the patent-holder. Moreover, with respect to possibilities of further development of patented inventions, there is a difference between upstream and downstream patents: licensing difficulties of the first may pose a hindrance to exploitation of the second, even though both are patentable as such. Some fear that the increasing number of upstream patents gives patent holders too much control on the downstream development and delivery of all genetic tests associated with a gene for a limited period of time.^{2,15}

There are concerns as to whether patent authorities appropriately interpret the patentability criteria. Clinical utility and validity of many granted patents have been reported to be deficient.¹⁵ Particularly, many of the patents have been broad in scope and the criteria for inventiveness

and utility have been weakly applied.⁵ The Nuffield Council report has, however, ignored the invention threshold and focused on novelty and inventive step, whereas the Danish Council of Bioethics Report in 2004 stated, that '... it cannot be said with any reasonableness that a sequence or partial sequence of a gene ceases to be part of the human body merely because an identical copy of the sequence is isolated from or produced outside of the human body.'¹⁸

The scope and interpretation of the research exemption is legally too uncertain to offer a sustainable solution to these problems.

The EC report of 2003 revealed that there are many deficits in genetic testing services in Europe.² The accuracy and interpretation of the results were not regarded to be at an acceptable level. It could be anticipated that the situation might get even worse if certain tests are performed exclusively in only a few laboratories, if tests cannot be validated and developed further, or if genetic testing services were moved to other territories for patent reasons.

Consequently, major concerns include how to access existing knowledge, whether patented or not, and how to be able to do research in the field of biotechnology, while at the same time not losing the patent system as an incentive for product development.

Many articles suggest that there is no adequate empirical data on the implications of genetic patents for policy-makers.^{1,11,19} In fact, not only the potential benefits, but also the adverse effects of these patents may have been overestimated particularly in the media.⁷

From a clinical geneticists' perspective, the main concern with respect to increasing patenting of genes is securing affordable access to diagnostic tools.^{9,14} There are often multiple mutations correlated with a particular disease. Before performing any genetic test, one must determine which mutations to look for. Problems arise, if several of the chosen mutations, SNPs, and mutational diagnostic tests have been patented by different parties. One of the feared consequences is that the costs of genetic diagnostic tests will greatly increase due to the accumulation of the many licence fees.

The aim of the ESHG

The aim of this joint document of the ESHG's PLC and PPPC is to explore how to achieve a situation where useful tests are available at affordable costs for diagnosis of patients. Despite already available recommendations and reports on gene patenting, the ESHG finds it necessary to focus further on diagnostics and public health aspects, and to define further action points to work with. With new knowledge constantly developing, such as ESTs, variants, gene expression mechanisms, genetic associations and so on, the practical framework is becoming more complicated.

The reason for focusing mainly on diagnostics (and not on therapeutics) in this paper is because diagnostic tools can be developed at relatively low cost, while development of therapeutic solutions requires lots of work, time and money. Consequently, the need to obtain return from investment seems to be much higher in the course of developing therapeutic inventions. Therefore, in the field of diagnostics a consensus of new solutions or alternatives to patents could be more easily discovered.

Though a thorough discussion of whether or not biotechnological patents should be granted in the first place is too involved for the scope of this paper, a few reflections on this issue are presented throughout.

The purpose of this background paper is to reflect on all possible views, and serve as a discussion paper, whereas the subsequently drafted recommendations will represent the ESHG's view in particular.

Methods of the study

The method used to produce this document was the systematic review of current literature and articles on patenting and human genes in major scientific journals. In addition, the recent reports and reviews produced by the international organisations (Organisation for Economic Co-operation and Development (OECD), Council of Europe, United Nations Educational, Scientific and Cultural Organization (UNESCO)) were studied.

The PPC and the PLC organised an initiatory meeting on 29 November 2005 in Paris with four external experts and a workshop on 13–14 November 2006 in Leuven, in which 18 experts were invited. Prior to the second workshop, each participant received a working document developed by the PPC and the PLC for further discussion. In addition, during the workshop, the participants were invited to provide statements or recommendations they considered as crucial to improving the field. The working document has become the background document; it aims at reflecting the discussions and various opinions.

Following the aforementioned process, the ESHG started to elaborate its own set of statements and recommendations. The draft recommendations were presented to the Board of the ESHG in June 2007.

A basic presentation of the legal framework, based mostly on national governmental websites providing official national information on relative national laws, is included in Appendix A.

Genetic testing in the clinic

Medical relevance of genetic testing

The aim of genetic services can be described as a response to the needs of individuals and families to know whether the presence of a certain disorder has a genetic nature, whether or not they are at risk of developing a genetic disorder or of bearing an affected child.²⁰ The detection of

genetic disorders is a complex process which requires special clinical evaluation, reliable diagnostic tools and expert interpretation of the results. In this process, genetic testing is a laboratory procedure detecting the presence or absence of, or change in, a particular gene or chromosome, including an indirect test for a gene product or other specific metabolite that is primarily indicative of a specific genetic change.²¹

Interpretation of the genetic test result is difficult. Sometimes a single gene may contain hundreds of different mutations, any one of which might result in slightly different clinical outcomes or have no effect at all. In other cases, more than one gene can cause what might appear clinically to be the same disease. Moreover, multifactorial diseases result from the interaction between a scattered variety of genetic predispositions caused by changes in several genes and environmental factors.

Over the past decade, nucleic acid testing has increasingly become an essential routine tool of clinical diagnosis and expectations for new generation assays are high. Most diagnostic laboratories are reported to use a combination of different methods (eg kits, homebrew methods, mutation scanning platforms or sequencers) to provide rapid and appropriate services.²² Some centres, however, have developed methods that go beyond DNA, such as the study of mRNA, either in real-time (eg the quantitative RT-PCR), or using RNA expression microarrays (transcriptomes), but also for proteins by protein microarrays.²

At present, medically relevant genetic testing can be regarded as an integral part of health service provision and can significantly improve an individual's life quality due to knowledge of the disease and its treatment options.^{20,23} For the purpose of this document, the term 'genetic test' will be used only as medically relevant genetic tests. However, it should be emphasized that not all genetic tests are truly diagnostic, since their diagnostic value varies according to the context in which they are used diagnostic vs non-diagnostic test results.

Once a link between a disease and a precise genetic defect has been established, the respective diagnostic test can be relatively easily developed. Most laboratories use a combination of different methods: either kits or relatively simple home-brew detection methods for the identification of one or a few mutations, or high-throughput scanning platforms or direct sequencing for the effective scanning of the coding regions of a gene. The ease of development of genetic tests has allowed diagnostic laboratories to rapidly provide appropriate services. Drawbacks of this ease include the resulting diversity in the services being offered and the potential lack of validation of the diagnostic methods.²²

Clinical utility and validity

A genetic test used in health care should meet certain criteria, for example it should be relevant and have clinical

validity and utility.^{2,24} The concept of clinical utility relates to the fact that a test should be beneficial for the tested person and in addition, if the benefit is established, the benefit should outweigh potential harm. There is an extensive on-going debate about whether: (i) clinical utility should be proven prior to the market approval of the test; (ii) the patent system is impeding the assessment of clinical utility; (iii) the patent system could be an incentive for more work on clinical utility, for example by restricting patents for methods of diagnosis to situations where the utility of the genetic test has been characterised.

According to the EC report on genetic testing services,² tests developed as research tools have been rather rapidly adopted as clinical tests, even though the proof of clinical utility has been insufficient (eg haemochromatosis). Fortunately most are diagnostic tests for rare monogenic conditions which are extremely useful as diagnostic tools for the patients and their relatives. Many of the patents which have been filled in, however, are also related to genes contributing to common multifactorial disorders. For these, the clinical utility of the tests to be developed is likely to be low or very low.

Genetic testing in relation to the clinical diagnosis

The clinical utility and validity of a genetic test should be evaluated in terms of its relevance to the clinical diagnosis. Clinical diagnosis, *in sensu stricto*, is based on abnormalities found through a genetic diagnosis in the individual's physical, mental, functional features, as well as findings from non-genetic diagnostic tests (referred to hereafter as 'clinical conditions') if the clinical condition fits into the definition of a known disease.

A genetic test may confirm a clinical diagnosis only if the disease is a known, described, monogenic or chromosomal disorder with evidence-based association to a disease-causing mutation. If no disease-causing mutation is known, genetic testing cannot confirm the clinical diagnosis, although some tests may support or weaken the clinical suspicion (eg HLA typing in patients with symptoms of HLA-associated diseases).

More importantly, in common complex disorders, genetic testing cannot confirm the clinical diagnosis, in spite of an increasing number of observations supporting an association of certain gene variant to genetic susceptibility. Genetic testing in such situation may contribute to the assessment of the individual's risk to certain diseases with slight–moderate–strong genetic susceptibility without clear confirmation of the clinical diagnosis.

The lack of evidence-based association between single gene mutations and the clinical condition, in particular in multifactorial diseases, makes the evaluation of clinical validity and utility difficult. The high rate of fruitless susceptibility test studies for common complex disorders results mostly from poor delineation of phenotypic/

clinical features of these conditions. Hence, the clinical utility and validity of susceptibility genetic testing, at least at the present state of our knowledge, is low.

Genetic testing was performed.

Diagnostic vs non-diagnostic test results

A genetic test for a clinical condition may be offered to (1) patients with a certain disease or symptoms/abnormal features (patients), (2) healthy individuals with no symptoms, or (3) embryos/foetuses whose clinical condition is not (or hardly) known. It is important to emphasize that an abnormal test result as such is not equivalent to a clinical diagnosis. The result of genetic tests should always be linked with the associated clinical condition. It is unhelpful to convey an aberrant DNA test to an individual without relating the aberration to a definitive clinical condition.

Accordingly, the diagnostic value of genetic testing should be evaluated in the context of the clinical condition as follows:

- in patients including embryos/foetuses, may
 - confirm or exclude a clinical diagnosis of monogenic or chromosomal disorder (there is an evidence-based association with disease causing mutation – the test result is diagnostic)
 - support or weaken a clinical diagnosis of multifactorial disorders (there is no clear association with single disease-causing mutation – the test results are not diagnostic)
- in symptomless individuals may
 - foretell or exclude a later-onset monogenic disorder (presymptomatic testing – the result is usually diagnostic)
 - contribute to risk assessment for common complex diseases (predictive testing – the test results are not diagnostic)
 - confirm a genetic state which is not known to have any consequence to the health of the individual, however, may confer a risk of abnormality in the offspring (heterozygote testing which is mating-dependent – not diagnostic)
 - discover an individual reaction type to certain drugs (pharmacogenetic testing – not diagnostic)

Laboratories

Genetic testing laboratories have developed in most countries usually nearby the clinical genetic services and most are located in the public sector.^{2,25} Public hospitals and research laboratories offer tests for clinically complex, newly characterised or difficult-to-diagnose rare diseases, whereas commercial laboratories provide the more common tests, based on stable technology, for which the clinical diagnosis is more straightforward.²⁵ Small local

laboratories tend to use validated and cheap commercial kits and processes to identify the most frequent mutations.²

In the majority of the cases the laboratories develop, assemble and perform their own in-house tests; only 14% were reported to rely entirely on commercial kit systems,²⁵ which often are kits required to detect fixed point mutations or copy number variants among the population. In the future, high-performance platforms, such as micro-arrays and gene chips are expected to improve the routine mutation scanning drastically.

Costs of genetic testing

The average cost of a genetic test has been estimated around 573 euros,² though great variations exist. It is not known how much of the cost of kits represent royalty fees, or to what extent the patents prevent development of in-house assays.

Many laboratories, especially in the United States, have reported to have stopped using certain genetic tests due to high licence costs.⁸ In Europe, genetic services are mainly paid by the public health care system,²⁰ so society as a whole also struggles with the increasing costs of licence fees. Reach-through claims, dependent patents, royalty stacking and licensing practices are feared to increase the costs of the end products (problems relating to patents). On the other hand, competition and development in the field have diminished the costs of many tests.

Genetic testing and patents

Patents on diagnostic gene tests based on DNA sequences, *per se*, have been questioned because the inventions usually concern knowledge of an association between a gene variant and disease; thus, they are to be considered discoveries.⁵ One serious problem of sequence-based diagnostic gene patents stems from the fact that unlike in many other fields, these are difficult to 'invent around', that is, to invent an alternative test by using a different method. Thus, the patent holder essentially has a monopoly over all ways of testing for the specific disease in question. The Nuffield Council raises the question whether it is in the public's interest that there is only one diagnostic test available for a particular disease. This stalls further test development. It is feared that quality of testing could be jeopardised through restrictive licensing^{2,8} because few clinics can use a diagnostic test subject to patent protection, research and improvement of the tests will be impeded.²⁶

Results of scientific research indicate that human DNA has more variation than previously thought. This variability should be included in the definition of DNA, emphasising that the genome in its natural state is highly variable. It follows that discovering a new allelic polymorphism or variation may have medical relevance and be regarded as invention only if its association to well defined

clinical condition and/or therapeutic consequence is proven by evidence-based and reproducible observations. This evidence-based support usually takes many years.

Example cases

There are various cases which differ in the extent of the patent holder's monopoly power, the availability of substitutes, and the bargaining power of the users and/or other stakeholders. It is worth noticing that these are the most commonly referenced single cases and the knowledge of gene patents' effects requires more evidence, as indicated in the introduction (see also Societal and Economical Aspects). They do, however, illustrate the current concerns. In addition, it is possible that the media coverage has mitigated the problems by forcing the actors to more cautiously assess their practices.^{7,27}

Breast cancer is relatively common, but differentiation between hereditary and non-hereditary breast cancer is often difficult. Hence the importance of the practice of genetic testing of BRCA1 and BRCA2, when hereditary breast cancer is suspected in the family. The 'discovery' of the familial BRCA1 gene was preceded by a large international collaborative effort with hundreds of breast cancer families in the early 90's. The first to apply for a patent, however, was Myriad Genetics in 1994 who tried to enforce its patent rights rather aggressively.²⁸ For example, Myriad's policy not to license the test further or at least not at conditions that were acceptable to the laboratories,²⁹ requiring that all the tests be performed in its own laboratories in the United States, upset the medical community in Europe, and inspired political resistance and mobilised opposition to the patenting of genes in general.^{28,30} There was effectively no substitute, and while Myriad had huge market power, users had no bargaining power. Most European laboratories find no other solution than to continue performing BRCA tests for their patients, in fear of being sued for infringement, since the cost of the test would have made the test practically inaccessible. After the strong opposition process in the Europe, the first patent on BRCA1 was revoked and the other two limited in scope (EPO Press release 25 January 2005). Similarly, the BRCA2 patent claims have been amended (EPO Press release 29 June 2005). At the time of writing this publication, appeals against the different decisions have been filed. The final decisions are thus pending.

Cystic fibrosis (CF) is the most frequently lethal recessive genetic disorder. The identification, in 1989, of CF gene was a prime example of 'reverse genetics' or positional cloning. A large international collaboration had led to the localisation of the faulty gene to chromosome 7, but it took several years to explore the region of this chromosome to identify and clone the CFTR gene. Once the gene was identified and its sequence was known, it became possible to test patients for mutations in this gene. Diagnostic laboratories and companies have developed kits for the

simplified identification of the most common mutations. The difference between these kits resides in the technology at the basis of the kit (which is often the proprietary right of the manufacturers) and not in the sequence interrogated for the mutation. The CFTR gene was patented by the Hospital for Sick Children of Toronto and the University of Michigan. The patent-holders have granted free access to gene sequences for diagnostic testing using commonly available technologies for mutation analysis, but have collected royalties on gene-based commercial test kits and from companies that offer commercial testing.

As a result, different kit manufacturers are competing and are gradually improving the sensitivities of their assays. In the mean time, CFTR testing has become widely available at a reasonable cost. It seems that the genetic or medical community has no major objections to this licensing model. However, the fraction of the cost of the kits that represents royalty fees is not publicly known. It would be interesting to know such figures to get an idea of the 'value' of a gene or mutation in intellectual property terms.

A third approach has been taken by Bio-Rad, the company that acquired the patent on the hereditary *haemochromatosis* (HFE) gene after Mercator Genetics went out of business. Haemochromatosis is a common autosomal recessive disorder characterised by an excessive deposition of iron in the tissues. The gene was cloned in 1996 and two mutations are responsible for the majority of cases. According to Merz *et al*³¹ the company offered to license laboratories to perform testing, but at a cost that makes Bio-Rad's own commercial test kit more economically attractive due to up-front payments and a per test fee of \$20 for two mutations. Thus the owner of the United States patent on HFE uses a very rigid licensing policy. As a result, many companies have refrained from developing their own kits for the disease. In the mean time, a European patent has also been granted, but few in the diagnostic community appear to have been notified by the patent holders. As there were no alternative tests, the company had a huge market power (as in the case of BRCA1) though soon other firms obtained bargaining power and forced invalidation.

A fourth example involves patients and families contributing to research projects aimed at finding new genes and diagnostic tests or recombinant drugs. The parents of children suffering from Canavan disease allowed researchers at the Miami Children's Hospital to use their children's samples to improve diagnostics and treatments for other children. The parents had collaborated actively with the researchers to collect samples and to build a register. The hospital researchers later developed a test by using the samples from the children and patented it without the consent of the parents. The parents acted altruistically and had wanted the information and the test and development of a cure to be freely available to all. When

the parents found out that the hospital had commercialised the results and had charged rather high costs for diagnostic tests and treatment, they pressured the hospital by starting court procedures until the centre halved the cost in a court settlement. In this case, the parents had bargaining direct power in the availability of a RD diagnostic test (Greenberg *et al* v. Miami Children's Hospital Research Institute *et al*, 264 F Suppl 2nd 1064 Florida District Court, case settled).

Ethical aspects of patents

General

Initially biotechnological patents were objected on grounds that they 'patent life'. By definition, however, although a gene may be sequenced or identified using the biological tissues of individual patients, the patented product is a non-living piece of information concerning a genetic substance.³² Moreover, 'sanctity-of-life' arguments were presented to support the idea of violation of human dignity by such patents. Also, the novelty and the nature of invention of genetic patents were questioned as they relate to materials already existing in nature.³³ Some find analogy of the long history of patents on naturally occurring chemical compounds to support the genetic patents. Others, however, say that this analogy ignores the fact that DNA is not merely a molecule(s), but is biological instructions for building specific proteins.

The prevailing question remains whether anyone should have an exclusive right to genes. The idea of gene patents is in severe contradiction with many people's sense of justice, morality and reality or with their perceptions of human dignity, genomic inheritance and common interests. A human gene or a part thereof is seen as a natural phenomenon, and as such can only be discovered, not invented. Isolation or other processes to handle a gene do not change this fact. It has been notably argued that although knowledge about a natural gene is not covered by a patent for its cloned and isolated sequence, any use of information on the gene would infringe on the patent for its clone.³⁴ Consequently, many countries and people consider the wordings of Article 5 of the European Commission's Biotech Directive (98/44/EC) a semantic game.

The French Bioethics Committee (CCNE) has listed three core ethical issues around biotech patents: (i) non-commercialisation of the human body, (ii) free access to genetic knowledge and (iii) sharing genetic knowledge (CCNE avis no 64 – 2000).

Human dignity and non-commercialisation of human body

The Biotech Directive (98/44/EC) acknowledges that patent law must be applied so as to respect fundamental principles safeguarding the dignity and integrity of the person, and

refers to these conceptions as adapted in the Council of Europe Human Rights Convention (1950). For instance, the ESHG has in the context of the BRCA gene patents expressed its concern about patent claims that have reference to racial, ethnic and familial origins. The patent owners have explored the limits of patentability, when they specified 'for diagnosing a predisposition to breast cancer in Ashkenazi-Jewish women' in the claim, to save the patent. On the other hand, one could ask why such characteristics should not be mentioned.

But do genetic patents violate the nature or human dignity, treat human beings as merchandise or violate someone's personal integrity? It is often stated that a person is more than a sum of his or her genes. However, it could also be argued that the personal integrity does not consist only of the 'sum', but also of specific traits which in some cases are determined by genes in such a way that it may threaten the integrity of the individual. Respect for individual autonomy requires that the person, whose body parts are used in an invention, has been given appropriate information and, based on the information, has consented.³⁵

The European Council Biomedicine Convention from 1997 provides that 'The human body and its parts shall not, as such, give rise to financial gain'.³⁶ This provision is basically meant to concern commerce and trafficking of human organs and tissues. Remuneration of expenses to blood or germ-cell donors is however usually allowed. The rationale behind the non-commercialisation is twofold: first, the human body shall not be instrumentalised, and second, it aims at protecting those who in the lack of other resources would sell their tissues and organs to get money. Patenting was not considered while drafting the Convention, but some argue that the principle of non-commercialisation of human body cannot be interpreted as hindering patenting.³⁷

Informed consent of an individual

A doctrine of informed consent is supposed to protect an individual's integrity. The informed consent of a research subject is one of the most established fundamental provisions of research regulation and medical law: research without appropriate consent is prohibited and also criminalised in many countries (eg data theft in the UK, research breach in Finland etc.). With a reference to Article 5 (b) of The Universal Declaration on the Human Genome and Human Rights (1997), the International Bioethics Committee (IBC) of UNESCO has demanded for scrupulous compliance with this universal ethical principle.^{6,38}

Recital 26 of the Biotech Directive (98/44/EC) prescribes performing the informed consent procedures with the person whose samples will be used in a biological invention. Even though there is some confusion as to whether or not a recital to a Directive is obligating, it has been strongly recommended to inform the research subject

also of the potentiality of a future patent to secure the validity of the potentially granted patent.³⁹⁻⁴²

People involved in medical research usually have altruistic motives, like for instance the parents in the Canavan disease case described earlier in this text. They did not seek benefit, but they did not approve that the results were patented and sold. Many refer to this case when arguing that people want to have control, which they can basically use by consent provisions.

The provision of the informed consent is supported by Recital 16 of the Biotech Directive stating that patent law must respect the dignity and integrity of the person and by Recital 43 requiring respect for human rights. The provision of informed consent was reportedly not included in any of the articles of the Directive due to heavy lobbying of the biotech industry.^{33,39}

One of the issues in the famous Moore's case in the United States was lack of informed consent and the court ruled that patients should be secured the right to control the use of their bodies and be given all the relevant information for consent. In this case dating back to the 1980s, a patient called John Moore suffered of a rare hairy cell leukaemia and his spleen was removed. While treating him, the doctor also developed a cell line from Moore's very unique cells without Moore's knowledge and consent. The doctor also kept asking Mr Moore to come for checkups to develop the cell line further and still did not indicate his purposes to Mr Moore. Subsequently, the doctor applied for a patent and sold it to a drug company. When Moore found out about this, he sued the doctor, the drug company and the University Hospital on the grounds of, *inter alia*, violation of his proprietary rights. This argument was revoked. However, the claims on the breach of the fiduciary duty and lack of informed consent were approved by the Supreme Court of California.

The openness and adequate information is crucial to maintain the public trust in research and get people recruited also in the future. Sufficient information to the research subjects is the first step. But also, general empowerment of the individuals may be relevant, as true autonomy does not necessarily materialise by the established consent procedure. Some argue that individuals who provide samples for research are currently undervalued and underestimated even though the recognition of their importance has grown.^{33,43}

The European Court of Justice, however, has reiterated the scope of the Biotech Directive to be restricted to laying down the principles applicable to the patentability of biological material and the extent of protection. Subsequently, the EC report of 2002 concludes that the Directive may therefore not regulate the informed consent which remains governed by national laws. The Advocate General emphasized the fact that the Directive does not attempt to regulate the use of biotechnological invention but rather their patentability. He argued further that 'the action

moreover highlights the importance of regulating at a national level the use of biotechnological material, precisely because such use, since it falls outside the parameters of patentability, is not – indeed cannot be – regulated by the Directive. In particular, adequate provision must be made for ensuring that the principle of informed consent is respected whenever material is taken from human beings which might be used for scientific or technological purposes' (Point 228 in Advocate General Jacobs' opinion to the case C-377/98).

The requirement of informed consent was removed from the articles of the Biotech Directive. As long as there is no clear obligating provision in patent law of an informed consent as a precondition for filing a patent, the notion of the informed consent only in the recital leaves the situation rather ambiguous. The recitals, as such, are usually not considered to have clear normative value, though they may become normative through court praxis. Furthermore, recitals indicate the purpose of directives which member states are obliged to consider when applying them. For instance, the EPO will not check whether the consent procedures have taken place. Therefore, the only way to test whether an invention was developed and patented without proper patient consent is to test the case in a national court. The outcome, however, is insecure.

Benefit-sharing

More and more voices are heard in favour of benefit sharing, which means that benefits resulting from the use of human genetic data, human proteomic data or biological samples collected for medical and scientific research should in some way be returned to society and/or groups of people involved in research. UNESCO^{21,44} has listed following ways to do this:

- (1) special assistance to, and acknowledgement of, the persons and groups that have taken part in the research;
- (2) access to quality medical care;
- (3) provision of new diagnostic and therapeutic modalities or products stemming from research;
- (4) support for health services;
- (5) access to scientific and technological knowledge;
- (6) capacity-building facilities for research purposes;
- (7) development and strengthening of the capacity of developing countries to collect and process human genetic data;
- (8) other forms consistent with the declarations.

The Declaration of UNESCO on Bioethics and Human Rights,⁴⁴ accepted unanimously at UNESCO's General Conference held in October 2005, addresses this issue in Article 15 by stating that 'benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international

community, in particular with developing countries.' Of particular relevance is that it also mentions new diagnostic and therapeutic modalities or products stemming from research. This article is almost identical to Article 19 of the International Declaration on Human Genetic Data.²¹ The Universal Declaration on the Human Genome and Human Rights³⁸ also claims that advances in biology, medicine and genetics shall be made available for all (Art. 12).

The consultants to WHO (2003)⁴⁵ insisted that some benefit should be returned to the individuals or groups involved in development of diagnostic tests or new therapies, if the important new knowledge has accrued from a certain population, or family, promoting cooperation from other groups in the future also.

The Bermuda Statement (1996) of the Human Genome Organization (HUGO)⁴⁶ proclaimed that the human genome is heritage of humanity and demanded free public access to the genetic information from public projects. Furthermore HUGO has given an explicit statement on benefit sharing in 2000, recommending, *inter alia*, that 'all humanity share in, and have access to, the benefits of genetic research'.⁴⁷ However, HUGO also acknowledges that researchers, institutions, and commercial entities should have a right to a fair return for intellectual and financial contributions to databases. HUGO introduced a model in which profit-making entities dedicate a certain percentage (eg 1–3%) of their annual net profit to healthcare infrastructure and/or humanitarian efforts.⁴⁸

Consequently, benefit sharing ideology is largely supported by the global community of policy makers. However, more practical initiatives are needed to demonstrate how exclusivity of genetic patents fits into these proclamations of benefit sharing.

Morality and *ordre public* clauses in the legal instruments and some court cases

Both the Biotech Directive and the EPC contain some moral rules that may exclude patentability. According to the Biotech Directive, inventions are held unpatentable, if their commercial exploitation would be against *ordre public* or morality. The old legal concept of *ordre public* refers to protection of important public interests (eg security, peace, democracy. For a complete definition of *ordre public*, see the Glossary at the end of the document). However, prohibition in law or regulation alone does not make the commercial exploitation of an invention contrary to *ordre public* or morality. The Biotech Directive lists some processes that shall be considered unpatentable, namely cloning human beings, modification of the germ line identity of human beings, uses of human embryos for industrial or commercial purposes, and modification of the genetic identity of animals if it causes them suffering without substantial medical benefit for human being or animal. The fact that germ-line modification is also banned for therapeutic uses may prevent industrial interests to

developing cure and diagnostics to specific diseases, such as for example mitochondrial diseases.

According to the morality provision in EPC, inventions, the publication or exploitation of which would be contrary to ordre public or morality, cannot be granted a patent. Exploitation of an invention shall not be deemed as against ordre public only because it is prohibited in some or all of the EPC states. The textbook example of an immoral invention is (still) the 'letter bomb'.

Patent law is generally held as neutral, meaning that patent authority does not have to pay attention to the consequences of the patent. Contemporary and local perception of morality varies even in Europe, for example regarding the beginning of life and hence embryo research. Therefore, an invention cannot be immoral just because some people do not like it, but only if it is deeply offensive to the great majority of the population.¹³

Likewise, consideration of economical consequences of the prospective patents falls outside the EPO's authority, that is, the fact that a patent might cause harmful economical consequences to some third party is not a reason to deny a patent protection.

Has or should patent authority have a function as a moral gatekeeper? The Nuffield Council on Bioethics⁵ states that assessing issues of morality or public order require philosophical, ethical and other expertise not available in a patent office. This view is supported by the argument that morality provision in EPC is 'ill-placed', because, first, the ordre public provision cannot prevent someone doing something unethical in the first place. Second, a patent authority should not have power to direct the innovation policy.⁴⁹ A counterargument could be, however, that the patent system should not support clearly unethical practices either. Line drawing is, of course, a difficult task. Finally, it shall be recognised that a patent, even in force, does not yet justify its use. The use of a patent must comply with other regulations. As the US Patent Law does not have morality provision, the European morality provision has been interpreted very narrowly to prevent innovations to leak elsewhere.³³

In the case of the 'Harvard-ONCO-mouse', cancer-prone mice were finally granted a patent, because the benefits for human beings outweighed the suffering of the mice (Harvard/ONCO-mouse (1991) EPR 525). However, claims to other mammals were declared invalid for being contrary to ordre public and morality.

One of the landmark cases concerning the use of human genetic material is the opposition procedure of a patent granted on 'the H2 Relaxin' protein (Howard Florey/Relaxin (1995) EPOR 541). The isolation of the protein had required removal of tissue from pregnant women. The involvement of pregnant women was considered immoral by some opponents, because, *inter alia*, the commercialisation of the vulnerable state of pregnant women was seen as violating human dignity and would result in 'modern

slavery'. However, the Opposition Division pointed out that women had given informed consent and no woman would be enslaved by this particular patent. The aspect of human dignity was not addressed.

It has been suggested that the EPO should take measures to clarify the interpretation of morality provision,^{5,50} and that it should seek general guidance from the European Group of Ethics (EGE).⁴¹ It could, for instance, disclose its considerations and decisions every time it has had to try this provision.

The IBC has proposed that World Trade Organization (WTO) should clarify that in accordance with the provision of Article 27(2) of the Trade-Related Aspects of Intellectual Property Rights (TRIPs) Agreement, the human genome is not patentable on the basis of public interest considerations set out therein, in particular, public order, morality and the protection of human life and health.⁶ IBC recommended several ways of creating an ethically sound approach to the issue of intellectual property and genomics. In the lack of progress, IBC stated that it will consider the feasibility of recommending a global moratorium on the grant of further patents in the General Conference of UNESCO. However, since the human genome is at the open net, the human genome as such is no longer novel.

In conclusion, so far ordre public and morality arguments have been approved only in very rare cases in the EPO.

Suggestion to establish an ethical advisory board at the European level

According to Article 7 of the Biotech Directive, the EGE⁴¹ evaluates all ethical aspects of biotechnology. Recital 44 stresses, though, that EGE may be consulted only at the level of basic ethical principles. The EGE has indicated the need for ethical evaluations in the course of the examination of the patent applications when they involve specific ethical dimensions (point 2.10), and expressed a wish that such an ethical evaluation will become part of the review process of the national patent offices or the EPO. For this, EGE suggests the establishment of an independent advisory panel. It is questionable though, if it is possible to reach common European values in the field of biotechnology. Moreover, the patent offices are not very keen on the idea, as they want to remain primarily technical evaluators.

When implementing the Biotech Directive, Norway established a national Board of Ethics to advise the Norwegian Patent Office when there is a doubt whether a commercial exploitation of an invention is compatible with morality and public order.⁵¹

Patents

Patents and patent-holders

The rights conferred by a patent are defined in a sort of a negative way: for example, a product patent shall confer on

its owner an exclusive right to prevent third parties, without the owner's consent, from the acts of making, using, offering for sale, selling, or importing for these purposes that product. This right requires active monitoring from the patent holder. A patent holder can allow third parties to use the invention by granting licences on his patent.

A patent holder, or anyone having a licence to a patent, needs to comply with many other rules and regulations concerning the invention; hence, it is possible that the invention may not be exploited.

The life span of a patent right may be divided into constitutive acts, consequential acts and terminating acts. Constitutive acts comprise filing, examination and granting; consequential acts are exploitation of rights and protection against infringements as well as capability to grant licences; and terminating acts are expiration after 20 years, revocation for example due to unpaid fees or successful opposition.

A granted patent has a life of 20 years from the date of the patent application. In some countries, it is possible for patents over pharmaceutical substances to be extended for a period of up to 5 years beyond the standard term of 20 years. Patent applications *per se* have no legal standing in terms of exclusivity of exploitation. As the grant of a patent occurs years after the application has been filed, the patent holder's exclusive rights are backdated to the date of application. Filing procedure may take several years, and the value of the application may drop or sharply fall in the meantime. The system is too expensive for many to hang along and further research may prove the filed invention not to be worth patent protection. It is anticipated that some of the patent applications are not even meant to lead to a patent. This 'strategic game' confuses the community even more.

Many inventors first carry out novelty searches and business feasibility studies before they apply for a patent. Maintaining the patent protection is expensive. Decisions on whether or not to apply for a patent will also differ if the control of infringements would be impossible, or if the need for protection is short-term. When a fresh invention is at hand, it may be wise to examine its potentiality first and file an international application under the PCT claiming the priority (see Appendix A).

For a historical perspective of the patent system, see the thorough report of the Nuffield Council.⁵

Different kinds of patent claims

Categories of claims include product claims and process claims. Usually an invention needs several claims to achieve proper protection (see the EPO Examination Guidelines 1978).

A product claim includes a substance or compositions (eg chemical compound or a mixture of compounds) as well as any physical entity (eg object, article, apparatus, machine,

or system of co-operating apparatus) which is produced by a person's technical skill. A product patent covers also prospective new uses of the invention, even if not foreseen at the time of patent application.

A process claim is applicable to all kinds of activities in which the use of some material product for effecting the process is implied; the activity may be exercised upon material products, upon energy, upon other processes (as in control processes) or upon living things.

A process patent covers also the product directly obtained from the patented process. On the other hand, if the same product was achieved by using another, non-patented method, it does not infringe the process patent. A DNA sequence can be 'used' in a process or method. In that case the invention (as defined in the claim or claims) limits the patent-holder's exclusive rights to the 'use' of the DNA sequence in that process or method.

Only a product claim can assert rights over DNA sequences themselves, whereas a use patent claim covers the use of the sequence. A broad use claim may, however, block the access to the DNA sequence itself. Therefore, the Nuffield Council⁵ suggests that narrow use patents on specific diagnostic tests might provide an effective means of rewarding the inventor while providing an incentive to others to develop alternative tests. However, from a (molecular) genetic viewpoint, this may be misleading: alternative tests will involve different or novel technology – which can indeed be inventive and become a proprietary tool – but all these methods still 'interrogate' the same genetic sequence, that is, they are only alternative methods to obtaining genetic data. For instance, all the methods listed in the Myriad Genetics' diagnostic patent EP 699754 (now revoked, but for different reasons) were established methods at the time of filing. The Myriad patents included use claims which were just as difficult to design around as the DNA product claims.

Patent application

To obtain a patent, the applicant must file an application in a national patent office or follow international procedures, with for instance, the EPO. The application shall contain clear and concise patent claims, as they will define the exact scope of the patent once granted. One patent application may contain dozens of claims. Claims may, however, be subject to changes during the process.

Claims are supported by an explanatory part containing description and drawings. The invention shall be disclosed sufficiently so that a 'person skilled in the art' could replicate it. In addition, in France and Germany, for instance, the purpose shall be presented already in the claim.

Priority date, for example date of filing of the patent application, is a date for assessing the novelty and inventive step in Europe. The situation is essentially

different in the United States, where the 'first to invent' principle is adhered to.

Patentability criteria

Only inventions can be awarded patent protection. The invention shall furthermore be novel, it shall be unobvious over the prior art; and it shall be industrially applicable (Europe) or show utility (USA) (see Introduction: definition of a patent). Discoveries are not patentable; although the terminology could be more defined (see the wording of the Biotech Directive in Appendix A).

The concept of an invention Concerning biotechnological patents, the term 'invention' is a very important patentability criterion. It must not be mixed up with inventiveness. An invention must solve a technical problem by technical means; it has to contain a technical contribution to the state of the art. A discovery is extending the scientific knowledge, whereas a patentable invention is increasing the professional skills; it is the technical application of the knowledge in a technical field. Of course, the association of a gene and a disease might well be a discovery at first. But the technical application of this finding may yield an invention. A non-patentable discovery and a patentable invention can be linked.

The mere isolation or characterisation of naturally occurring biological materials, such as DNA, does not satisfy the 'invention' threshold. Sequences can be isolated, cloned and replicated, and thus patented, whereas genes that appear and are expressed in the human body are in their natural environment and cannot be patented. Isolation as such is routine nowadays, so isolation of a gene alone is not (or no longer) enough. In England this is because an isolated gene is considered a mere discovery. In other countries the reasoning is that such claims lack an inventive step. This difference has practical significance.

It has been noted that patent terminology is often used quite loosely. The terms DNA sequences, copy of a DNA (cDNA), gene fragments, DNA fragments, DNA or gene fragment sequences, and cDNA fragments generally mean the same thing: a copy of a fragment of DNA containing the code for a portion of a gene.¹⁵ Nevertheless, DNA is usually claimed as cDNA, which does not contain introns, unlike the natural gene. Thus such a claim does not cover the gene in the body.

Novelty Novelty means that an invention presents something new not previously disclosed to the public. This criterion is very strict and may be jeopardised by any disclosure or leakage of knowledge prior to the application. In the United States, but not in Europe, the system offers a one-year grace period. The Biotech Directive states that when sequences overlap only in parts which are not essential to the invention, each sequence will be considered as an independent sequence in patent law terms.

Inventive step An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art. The prior art, that is, the level of technology is constantly changing, which increases the bar for the inventive step. Modern patents contain more industrial and sophisticated solutions than before. Prior art has changed drastically in the last 20 years; what was patentable then would not be today.

HUGO has expressed a concern that 'the patenting of partial and uncharacterised cDNA sequences will reward those who make routine discoveries but penalise those who determine biological function or application. Such an outcome would impede the development of diagnostics and therapeutics.'⁴⁸

The patentability of individual mutations, SNPs and gene variants is basically possible but controversial, and it is questionable as to whether in an isolated form they are patentable subject matter or 'inventions'. Their patentability requires assessment as to whether they are obvious or not, close to prior art, or present too much of an analogy between mutation and wild type, and so on. The same mutations may relate to several pathologies and could thus be found in several patents. Mutations can be patentable if they are shown to have an effect, mere probability is not sufficient. On the other hand, mutations relevant to predictive screening are patentable. One has to be able to specify which protein or part of a protein is produced or what is the function it performs. This is somewhat at odds with the observation that for many patented genes, the function of the gene product had not been identified by the inventors, let alone that the loss of function of a mutant had been documented, but was merely derived from its association with a disease. The only novelty is in the disclosure of the gene sequence itself, and that mutations in the gene are associated with for example, breast cancer.

On the other hand, a trilateral comparative study by the EPO, the JPO and the USPTO on protein 3-dimensional structure⁵² concluded, *inter alia*, that hypothetical claims to computer models of proteins generated with atomic coordinates, data arrays comprising the atomic coordinates of proteins, computer-readable storage medium encoded with the atomic coordinates, and databases encoded with candidate compounds that had been electronically screened against the atomic coordinates of proteins were not patent eligible (see ref. 52 for more details, www.trilateral.net).

HUGO has also pointed out that biological functions in the human genome are not limited to DNA sequences that encode proteins, but comparative genomics clearly indicates that 'regulatory, structural and catalytic functions can be performed by DNA sequences that are transcribed but not translated (ie non-coding DNA) and by genomic DNA directly (ie by sequences which are not transcribed)'.⁵³ HUGO emphasizes that it should be generally understood

that a claim on a DNA sequence does not extend to alternatively spliced transcripts if these have not been specified in the patent claim.

The Nuffield Council argues that while DNA sequences usually meet the criterion of novelty, the other criteria, inventiveness and industrial applicability, are often weakly met. They did not, however, analyse the basic notion of the invention. The Nuffield Council pointed out that data processing techniques are replacing cloning as the main route to identifying the genes, which needs reconsideration of patent criteria for DNA sequences. *In silico* processes, computational systems to identify genes are seen to diminish the inventive value.⁵ Furthermore some positive evidence of claimed utility should be shown, and it should be more than just a biological function as this would be only a description of a fact of nature, instead of practical utility. With respect to genetic tests, the Nuffield Council states that an association between a gene and a disease is not much more than discovery, and may not meet the criteria for patenting. DNA sequences contain genetic information which distinguishes them from other chemical compounds. As a conclusion, Nuffield Council recommends that the granting of patents that assert rights over DNA sequences should become the exception rather than the norm. Similarly, UNESCO states that knowledge, *in sensu stricto*, cannot be treated as exclusive intellectual property.⁵⁴ WHO consultants have stated, while acknowledging that patents may be necessary for funding to R&D of diagnostic and pharmaceutical products, that 'gene sequences without a proven utility should not be granted patents'.⁴⁵ Since publication of the human genome, such claims are in any case no longer novel.

Sufficiency Rules on sufficiency and support, that is, Articles 83 and 84 of the EPC, also require special attention. At least in Great Britain, these rules mean that the specification must enable the invention to be performed to the full extent of the monopoly claimed. If not, the claims must be narrowed in order to be valid. The rationale is that a patent holder cannot claim what he has not taught other skilled people to do. Or to put it another way, the claims and the specification must be commensurate. This rule has usefully blocked several overly broad biotech patents: see eg *Kirin-Amgen v Transkaryotic Therapies* (2005) RPC 9 (HL) paras 102–127 and *Biogen v Medeva* (1997) RPC 1. However the lack of legal certainty is problematic.

Industrial applicability Much of the discussion on inventiveness deals with a third criterion, industrial applicability. For instance, even though ESTs would be eligible for patenting, they have not been considered to fulfil the patentability criteria unless they have industrial applicability. Currently, EST patents are not likely to validly cover an entire gene.¹³ This has since been confirmed in the United States by a recent decision of the CAFC, (in re

Fisher, 2005) which denied patentability of ESTs for lack of utility. Utility is corresponding United States term for the European Industrial applicability, but not fully equal.

The industrial applicability criterion has not *de facto* required practical use in the earlier European legal context; potentiality had sufficed. This has been a problem in Europe, because not all the patents do lead to practical applications, but may still block further research. It has been argued that theoretical possibility is not enough: specific and real utility should be required. Aoki and Nagaoka⁵⁴ have identified conditions under which strong enforcement of utility requirement is desirable. Diagnostic use of gene sequences is likely to satisfy this condition in contrast to gene sequences in general. According to the Biotech Directive 98/44, a mere DNA sequence without indication of a function does not contain any technical information and is therefore not a patentable invention. There is, nevertheless, an important distinction to be made between a claim to a DNA sequence *per se* and a claim to a DNA sequence in a product, such as a diagnostic or medical apparatus or medicine. The nexus between the discovery or identification of a specific gene as a cause of disease and a claim that prevents anyone from using that gene in any form of diagnostic, is not clear and arguably is unjustified.

The Biotech Directive now explicitly requires that the industrial use of a gene sequence or its part shall be shown in the patent application (Art. 5(3)). Prior to the Biotech Directive, the Group of Advisers on Ethical Implications of Biotechnology to the European Commission (GAEIB) stated in 1996 that granting of a patent to a human gene or a partial sequence is acceptable only if, first, the identification of the function is attached to a gene or partial sequence allows new possibilities, and second, the intended use is sufficiently specific and identified.

In 2001, the Opposition Division of the EPO set the criterion for industrial application of a gene sequence as follows: the potential utilisation of a sequence disclosed in the application must not be speculative, that is, it must be specific, substantial and credible (Decision of the Opposition Division of 20 June 2001, *ICOS/Smith Kline Beecham and Duphar International Research*, OJ EPO 6/02, p.293). It may be useful but it is probably too early to evaluate the actual effects of this decision to the filings post to this decision. These criteria are lifted directly from the USPTO, and have no basis in the EPC. Nevertheless, they are sensible ones.

The equivalent of the industrial application or utility concept in the United States has also gained attention in 2001: an actual use of the invention must be shown (Utility Examination Guidelines, 66 fed Reg 1092-02 (5.1.2001); however, for United States critics, see Lopez-Beverage¹⁵).

Exemptions from patentability

Article 52 (4) EPC states that methods for treatment of the human or animal body by surgery or therapy and

diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application within the meaning of Article 52(1). This provision shall not apply to products, in particular substances or compositions, for use in any of these methods. Thus, a certain method or a way to perform surgery, give therapy or make diagnostic tests, does fall under this exemption. In contrast, a tool to perform these actions can be patented, such as a tool with a new technical solution to measure the body temperature, even though it serves diagnostic purposes.

It has been suggested though that Article 52(4) should be interpreted as to prohibit patenting of genetic diagnostic methods (ie identification of a mutation responsible for a disease).⁹ However, the Article 52(4) exclusion from patentability does not apply to *in vitro* methods of diagnosis (this is the effect of the word 'on'). Therefore, it has very little impact on genetic diagnostic tests. This provision has been subject to conflicting interpretations at the EPO. Upon the referral of the President of the EPO, the Enlarged Board of Appeal addressed this question and issued a thoroughly explained opinion G 0001/04 at the end of 2005 (EPO G 0001/04). It concluded that the exemption shall be interpreted narrowly: the diagnostic methods referred to in Article 52(4) EPC include the method related to the 'deductive medical or veterinary decision phase, that is, the diagnosis for curative purposes *in sensu stricto*, representing a purely intellectual exercise'. The Board of Appeal listed several features that will be required for the subject matter of a claim relating to a diagnostic method to fall under the exclusion from patentability. It argued further that due to the recent scientific developments and the multistep nature of genetic diagnostics a physician seldom has means to reach a diagnosis by his own methods, but requires complex and technically sophisticated means which can usually be accessed by acquiring the relevant kit or device. On the other hand, should he be able to reach the diagnosis by a non-patented method, he would not infringe the patent. Therefore, the Board of Appeal argued, an individual physician's possibility to perform his job will hardly be hampered by a patent protection of these methods. This argument can be criticised, however, by the negative effect of increased costs to the practice.

The EPC shall be revised in the near future and Article 52(4) will be removed. The new Article 53(c) will not however change the legal position and the interpretation of EPO Board of appeal will remain valid.

Still, the Biotech Directive expressly stipulates that 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. Many medical professionals and the public find it difficult to overcome the apparent discrepancy between this

disposition and the possibility to obtain a product patent for a DNA sequence.

Consequences of a granted patent Rights

The patent holder has a monopoly to decide upon the use of the patent. The patent holder may decide to use the invention himself or grant licences on different basis. In some countries, the monopoly is limited to professional and/or commercial use.

Sometimes he is also obliged to use the patent to avoid the granting of compulsory licences to third parties. It is however questionable whether a threat of a compulsory licence is generally an effective incentive on patent holders to be fair and reasonable in granting licences. Abuse of the monopoly position may also be intervened by competition regulation. (see below on competition Chapter on novel approaches).

Infringements

A patent gives its holder a right to prohibit others from using the patented matter without a licence. He may sue the infringers. This requires actions by the patent holder. The surveillance of infringements may be difficult, and litigation usually consumes much time and money. In some countries, however, intentional patent infringements are penalised. In Finland, for instance, a public prosecutor is obliged to plead a patent infringement in court upon request of the patent holder. However, this type of provision seems to be unusual.

Under Article 64 EPC, any infringement of a European patent shall be dealt with by national law. The process is currently very expensive and time-consuming, and can lead to situations where the same patent is held to be infringed in some EPC countries but not others (on the same facts). There is, however, an attempt to set up a European Patent Court to remedy this problem (see Appendix A).

Exempting a prior use

If someone has already used the invention before the patent application was filed, he may continue to use it. For instance, if some private laboratory had (in secrecy) developed a certain test by its own initiative, and another party files a patent for its own similar invention, the prospective patent holder cannot prohibit the use of the invention or demand royalties from the first one. This is not always so evident and suffers from the lack of clear rules. The prior use must be proven, which is not always easy.

Expiry of a patent

A patent may expire for several reasons. First, the patent holder is obliged to pay annual fees to keep the patent in

force in each country, which may become expensive. If the invention proves to have no value or is difficult to exploit without further development, the patent holder may decide not to maintain the patent. Second, the patent holder may become subject to an opposition process (see next page licence agreements (licensing)) and subsequently the patent might become revoked or amended and limited. Third, a patent may also be annulled in national court proceedings, for example, if someone sues the patent holder and claims a better right to the invention. Fourth, a patent expires 20 years after filing the application unless extended, for example by a Supplementary Protection Certificate in Europe. A patent holder may also notify the patent authority that it will waive the patent right.

Problems relating to patents

Reach-through claims, royalty-stacking By reach-through claims a patent holder may attempt to acquire royalty rights or other benefit from prospective inventions made by someone else with the use of the patent-holder's invention. The real problem is the breadth of claim. The broader the scope of the claim, the more the patent holder can exclude others from exploiting technologies that come within the scope of the claim and therefore the greater the patent-holder's negotiating position. The patent holder typically has an upstream patent to a research tool, that is, biological materials or methods, such as reagent kits, markers, assays etc. According to an OECD survey,²⁶ a research tool patent does not normally contain claims to products found by using the tool. Nevertheless, there seems to be a trend towards demanding downstream royalties from the sales of a medicinal product discovered with a research tool. The breadth of claim therefore encourages patent holders to seek to capture within the scope of the claim technologies which are further downstream. This would cause royalty stacking.²⁶ Royalty stacking means a situation in which the use of certain invention requires many licences from different patent holders, and thus increases the prices for end products.

EPO, JPO and USPTO have noticed the increasing number of reach-through claims and made a comparative study on how the patentability standards and examination strategies in the respective offices apply to these types of claims to enhance mutual understanding.⁵⁵ The study assessed different kinds of cases and reported rather similar views with regard to the claims that do not comply with one or more of the patentability requirements, that is, industrial applicability, utility, enablement, support, clarity and/or written description (see www.trilateral.net).

Dependent patents are also problematic and may lead to uncertainty or higher prices of the end products. If many patents are granted for inventions that claim respectively a partial gene sequence, the full-length cDNA or gene, and the protein encoded, it may be unclear which title holder will be able to prevent the others from the use of his

invention.²⁶ Furthermore, some fear that full-length DNA sequence patents may require a host of licences from the patent holders of ESTs or SNPs presenting in that sequence. This is however not a realistic vision as EST patents are invalid, and SNP patents cannot cover a full sequence (PW Grubb, personal communication). The use of a subsequent patent depends on the first patent: exploitation and commercialisation needs consent of the patent holder of the first patent. The first patent holder has absolute protection, whereas the second has usually, but not always, only purpose-bound limited protection. For example, a dependent patent may cover a group of products smaller than that claimed in a first patent ('selection invention'). As a rationale for this it has been stated that the second patent-holder has used the work of another to develop something. The counterargument is, however, that science is generally cumulative and builds on previous knowledge in all fields.

In this fashion it is easy to envisage how royalty stacking may hinder access to proteins, technology, promoters, determinants, isolation because of overload of licence fees due to many patents.

Product patents The problem with product patents is that under the current patent systems the protection may extend to all subsequently invented new uses, even if they were not anticipated in the patent application. Many acknowledge that it is reasonable that a test itself may merit protection, but not all the possible uses of the gene it is associated to. Genes have unknown functions, they can produce several proteins; introns can have independent functions, so called junk-DNA can be involved in regulating the genes and how and when genes are expressed. Many functions are still to be found. Therefore, product patents in biotechnology are not generally held fair and justifiably, and very stringent application of the criterion for inventiveness ought to be applied.⁵ In particular, the Nuffield Council supports opposition to product patents by arguing that in genetic tests it is usually an association that has been brought to light rather than the invention of a gene. Hence, it is the knowledge that becomes applied in the context of a test. But the dichotomy of invention and knowledge or discovery is not always that obvious.

It is questionable whether a valid patent can make claims to isolated DNA as products. See the UK Court of Appeal in Genentech's Patent (1989) and the House of Lords in Amgen v TKT (2004).

Defensive use Defensive patent policies, like for example, in the case of drug targets pose a general problem, as only a small part of such targets will eventually lead to a commercially exploitable invention. As already mentioned, there are very few such patents, although many patent applications. However, the mere fact that there are such applications pending might prohibit further research

and development of therapies based on this target. Therefore these are considered harmful.

Research tools Scientists need resources or research tools that have no immediate therapeutic or diagnostic value but are rather used in conducting scientific work. Research tools can be classified into three broad categories: research techniques, consumables, and targets.⁵⁶ Genetic research tools include partial DNA sequences or ESTs, SNPs, and other sequences that may be complete but where the function may not be clearly known, so they do not meet with the utility criterion. The Nuffield Council sees these as merely routine discoveries that seldom are eligible for patenting.⁵

Access to knowledge

In the field of biotechnological patents, many of the concerns actually do not relate to the patent system but rather to the access to (and use of) knowledge. The basis for biomedical research and current knowledge of genomics and genetics has been achieved in collaboration with public and private sectors, patients and families. Progress of biomedical research would require continuation of this tradition, but the situation has changed as competition has got harder, individual researchers (or groups) have selfish motives, research institutes and universities wish to have part of the benefits of patenting, companies practice defensive patent policy, and so forth (public research institutes and universities). Thus, even in the academic field, access to knowledge can no longer be taken for granted. IPR holders do not always fully exploit their rights and knowledge, but do not make it accessible to others either. Nevertheless, effective exchange of knowledge between those who research and those who develop new innovations is regarded as extremely important.

Access to the knowledge that is covered by business secrets is usually agreed by material transfer agreements. In case of a patented knowledge, the patent owner may grant others a right to use the invention by a licence.

There are several reasons why someone might not get access to the new patented technology he needs: (1) the patent holder does not want to licence it; (2) the licence fee is much too high; (3) the other terms of the licence are unacceptable; (4) the technology is covered with so many (dependent and/or crossed) patents that getting hold of them is utterly difficult or expensive. This list is naturally not exhaustive.

In the 'jungle' of many different patents and patent holders, one practical problem is that the users, and in the case of diagnostics, the clinical laboratories, do not know which licences, if any, are needed, who the patent holders are, and which methods are covered by a patent, so that they even could pay royalties. In such a situation, further innovation may be hampered. However, the EPO provides

a searchable database at the address <http://ep.espacenet.com> which on its part might ease this problem. In addition, the EMBL Nucleotide Sequence Database offers submission tools, data retrieval facilities and user support at www.ebi.ac.uk/embl.⁵⁷

The problem of anticommons refers to the phenomenon that only few finally can use the innovation, that is, it remains underused. Increasing amount of granted patents and defensive patenting policies of the companies may accelerate this problem. Nevertheless, despite years of speculations of this problem, there is still no evidence to show how real the problem is.^{7,27,58}

Foundational genetic invention is of major importance for further development. The OECD defines a foundational genetic invention as an invention that opens a new field of research or medical practice.¹⁴ If such inventions remained unlicensed, the research and medical practise might be slowed down. An example of a foundational invention that has been broadly licensed globally is PCR. Approximately 75% of United States laboratories have a licence to PCR.⁵⁹ The OECD wants to promote non-exclusive licensing of foundational genetic inventions so that they are broadly accessible.¹⁴

Licensing

Licence agreements

Licensing agreements are one form of disseminating knowledge that is protected by IPR, and they are usually beneficial to both parties. A research unit may lack practical possibilities and experience ongoing to sophisticated application of its invention, but by licensing the invention further it can gain return from its own input. The licences may be limited by for example, time, scope, area of activity and jurisdiction. The conditions are subject to a licence agreement.

Licensing is not very regulated and practices are not well known, even though few practices known thus far have been harmful. To clear up the situation, OECD has issued guidelines for the licensing of genetic inventions which contain principles and provisions of best practices on the manner in which licensing activity should be undertaken.¹⁴ OECD insists that licensing practices should foster innovation in the development of new diagnostic inventions and should ensure that therapeutics, diagnostics and other relevant products and services are made readily available on a reasonable basis. Licensing practices should encourage rapid dissemination of genetic information. OECD encourages broad licensing for research and investigation purposes, and particularly in clinical research and clinical practice.

One of the biggest problems with licensing is that often the terms are subject to confidentiality requirements. This makes it easier for patent holders to manipulate the market and licensees. OECD has set the principles of a mutual

benefit of parties, the licensor, that is, the one who grants the licence, and the licensee, that is, the one who obtains a right to use the invention on certain terms, should both obtain returns from the invention. However, licence agreements should avoid reach-through rights to enable utilisation and further innovations. Practices, rights and obligations should be as clear and certain as possible.¹⁴

The most common licensing policies

Exclusive licence By an exclusive licence, a licensee gets an exclusive right to use the invention and associated IPR. Even the licensor has no rights to use the invention itself or to license it further. This approach is not recommended in the field of genetics by the National Academy of Science (NAS),³ which is the highest advising body to Congress in the United States, for instance, who recommends that universities should retain the authority to disseminate their research materials to other research institutions and to permit those institutions to use patented technology in their non-profit activities. Exclusive licences may be anti-competitive, and thus, be subject to legal attack. In addition to competition issue, in case of very basic technology that require more research, limiting it to one research body could be risky.

Sole or semi-exclusive licence By a semi-exclusive licence, both the licensee and the licensor can use the invention. However, the licensor is not allowed to grant a licence further.

Non-exclusive licence Non-exclusive licence usually belongs to an active commercialisation and dissemination policy of the company. By a non-exclusive licence a licensor may accord a right to use the invention to several parties, but retains the right to use it and license it further. Accordingly, the licensee's rights focus only on the use. The economists' view supports the idea that broad non-exclusive licensing would maximise the use of genetic inventions. OECD wants to promote non-exclusive licensing of foundational genetic inventions so that they are broadly accessible.¹⁴

Licensing in diagnostics In the field of diagnostics, four licensing approaches have been particularly identified: (1) major research institutes have granted free access to gene sequences for diagnostic testing using commonly available technologies for mutation analysis, but collect royalties on gene-based commercial kits, (2) the patent holder offers licence to perform testing, but, in some cases, its own commercial test kit becomes cheaper than the licence fee, (3) exclusive licence policy, and (4) the BiOS licence (the Biological Innovation for Open Society), whereby the licensee, instead of paying royalties, must agree to share the improvements on the patented inventions.⁶⁰

What is reasonable licensing fee?

While acknowledging the importance to gain profit on investments, the OECD encourages licensing practices that are not detrimental to further research and development, and that make genetic inventions available on a reasonable basis at health care field.¹⁴ But what is a reasonable fee?

Licence agreements may contain different provisions to up-front payments and annual fees, regular royalties fixed on sales and so forth. OECD discourages up-front payments, that is, collection of a fixed basic fee, because it wants to promote low barriers for access to genetic inventions.¹⁴

The cost of a fee is directly linked to the problem of royalty stacking. As one solution, OECD suggests that licence agreements should include mechanisms to set a reasonable overall royalty burden for genetic invention products and services, including research tools. In more general terms, private and public sector are encouraged to develop mechanisms to decrease transaction costs in acquiring rights to use technology.¹⁴

One should note, however, that all things considered, the price of a licence might prove to be reasonable, when compared with the total benefit the access to the invention might bring along. Therefore, the disapproval and accusations of high licence fees should be put into the context: what is the alternative, if any?

There are arguments supporting the demand that licensing fees should be equal for all; one researcher or user not being favoured over the other. This might be regarded as desirable both in terms of competition law and R&D efficiency. From the point of view of efficiency, a fixed fee is better than a royalty, as the latter might increase the price of the end product and hence lead to its underuse. Since OECD discourages up-front payment, fixed fee could be proportional to profit, for instance.

Remedies within the patent system

There are many people who think that the problems indicated above do not actually stem from the patent system itself, but are rather a result of the new interpretations of the patent law when facing new and often ethically challenging techniques. They present the view that the patent system is self-correcting and should, therefore, not be intervened with. Instead, the key to solving the problems may be found in the patent system itself, because patent laws contain provisions such as opposition procedures, compulsory licences, research exemptions, morality clauses. However, there are others who think that the existing rules cannot respond to the problems, and actually the patent law does not at all fit into modern biotechnology. At least, to maintain the old system, solid evidence of its benefits should be acquired.⁶¹

Opposition and revocation

The EPO allows free access to anybody to survey pending patent applications or granted patents. This enables third parties to draw the attention of the EPO to certain issues they think are damaging to patentability, but without getting involved themselves (EPO Press release 27 October 2005).

Any third party may oppose a patent in the EPO within the 9 months after it was granted. According to Article 100 EPC, the opposition is possible on three grounds: (i) the subject matter is not patentable; (ii) the disclosure of the invention is not sufficiently clear and complete; and (iii) the scope of the granted claims extends beyond the content of the application as filed. The opposition procedure could take several years. According to Mr Pompidou, the President of the EPO, every year five percent of the patents granted are opposed, and in two-thirds of the cases, the patent is amended or even totally revoked (EPO Press release 27 October 2005). The opposition procedure is thus an effective tool to attack granted European patents. On the other hand, a patent holder can enforce the patent in national courts during the period of opposition.

The validity of a patent may also become tried in national court proceedings. Although the patent is granted by the EPO and applies to all designated EPC countries, revocation proceedings must be brought before a national court for each country. As the national conditions may vary, a patent may thus get a different treatment in different states. All this results in duplication in litigation, creates uncertainty with different courts possibly reaching different conclusions and is extremely inefficient and costly.

Research exemption

In the European context, research exemption usually means a possibility to an unlicensed use of patented invention in (pure) research with no commercial implications. However, many people think wrongly that the research exemption, also referred to as an experimental use exemption, allows further scientific research with the invention, whereas it usually only allows research *on* the invention. This however depends on the way the claims are written: for example do they claim clinical utility or diagnosis? *In sensu stricto*, the research exemption allows only for examination of the invention itself, but not any other use, whether it is commercial or not. Performing a diagnostic test, for instance, is no longer research on the invention. Indeed, the scope and limits of a research exemption are rather unclear and differently interpreted in Europe. Therefore some instances demand legal clarification to the situation (Danish Council of Ethics, 2004 Workshop 3),¹⁸ whereas others argue for maintaining the present situation, due to difficulties to define the scope and limits, and because too broad a research exemption might be counterproductive (OECD 2002, p. 59, 81).¹⁴ In a recent

working paper, the OECD has studied the research exemption and concluded the following: There is evidence that patents may have some deleterious effects on scientific research.⁶² A research exemption may be beneficial in some cases, and should be introduced in the countries that not yet have adapted it. However, such an exemption should be established in a way that encourages investment in non-commercial research, but should not adversely affect the returns on investment of the patent holder.

When is research just research and when does it have a commercial aspect? Even public health care is a huge economical activity. If they were not obliged to pay royalties for the use of new knowledge, the commercial sector could be seen as being forced to subsidise the public sector. In other words, the public sector could be seen as unjustly competing with potential commercial providers. Indeed, the general discussion seems to ignore that also clinical treatment, university research, and so forth constitute economical activities, regardless of the nature of public or private funding.

Nagaoka and Aoki⁵⁴ show that research exemption is particularly beneficial when the nature (commercial or not) of the final product is unknown. Patent owner can negotiate a licence if and when the final product becomes commercially viable. Exemption allows downstream researcher to do the research without a licence. This may prove to be effective particularly when inventing around is difficult.

It has also been suggested that governments should consider supplementing the research exemption by making free granting of licences to other public research institutions mandatory for everyone receiving public funding, similar to NIH's policy in the United States. Moreover, industry could create self-regulation containing the rules to grant a licence to public research institutions for a nominal licence fee.¹⁸

In conclusion, the situation regarding the scope of research exemption is unclear. There are variations both in legislation and interpretation in different countries.^{14,56}

Compulsory licensing

Compulsory licensing means the situation when an official instance or a court forces the patent holder to grant a licence to a third party. Basically, a compulsory licence is possible only in certain circumstances, as set out in the WTO TRIPs Agreement. It is not likely to be a free licence: the patent holder is still allowed to a reasonable fee and may use the patent himself as well. Thus, a compulsory licence is a sort of mandated non-exclusive licence.

The Biotech Directive does not address the issue of compulsory licensing other than regarding plants. The EPC also remains silent in this respect. The TRIPs (Art. 31) contains a limited provision that allows compulsory licences. Under this provision, one should first try to negotiate with the patent holder to achieve a voluntary

licence on reasonable terms. In case of a national emergency, prior negotiations are however not required.

Under Article 8 TRIPs, members may protect public health and nutrition and promote public interests on certain vital sectors, as well as prevent abuse of IPR or practices that harm trade or transfer of technology, as long as such measures do not violate the TRIPs agreement. The Doha Ministerial Declaration on the TRIPs agreement and Public Health (2001) affirmed that 'the TRIPs agreement can and should be interpreted and implemented in a manner supportive of WTO members' right to protect public health'. It continued that each member has the right to determine grounds upon which they can grant compulsory licences and what constitutes a national emergency or other circumstances of extreme urgency. This freedom shall be used in good faith, however.⁶³

The regulation of compulsory licensing lies to some extent in the hands of national laws and court practice. Most EU Member States, also members of TRIPs, have provisions in their laws for compulsory licences in the public interest. Even though the main focus of the Doha Declaration was to answer the problems of availability of pharmaceutical products in the developing countries, the principles as described above are of general nature. Therefore, member states have much flexibility to integrate social policy goals: they are allowed to grant compulsory licences in the public interest, as long as this happens in compliance with the TRIPs Agreement and other compelling regulation.⁶³

In many countries, a patent holder is obliged to exploit the invention within a country, under a threat that it may otherwise become a subject to a compulsory licence. For instance, in Finland and France, if the invention is not used within three years of the grant and within four years within the filing of the application, the one who wants to use may be granted a compulsory licence. In case of dependent patents, the patent holders may be granted compulsory licences to each others' inventions. Further, in case of a significant public interest, one who wants to professionally use certain invention may be granted a compulsory licence. These situations are covered by the Finnish Patent Law and by the French Bioethics Law (2004). In many European countries, similar situations are dealt with legally, in various ways.

When there are no possibilities to develop alternative diagnostic tests due to a genetic patent, Nuffield Council suggests that the resort to and the use of a compulsory licence is acceptable.⁵

It has been suggested in many forums that more extensive use of compulsory licences should be used if patent holders refuse to grant research licences at affordable price.¹⁸

Hence, compulsory licensing constitutes an important safety valve, but it may not offer a satisfactory solution in case of patent thickets. Compulsory licences are rarely used

so the practice and case law is lacking, which makes it unfamiliar to refer to. Furthermore, many countries will examine the demands for compulsory licensing only if the initial patent has not been used for several years which delays access to the invention significantly.

The assessment of adequate remuneration for compulsory licensing may require a distinction between those granted in the public interest and those granted only for competition reasons.⁶³

***Ex officio* licensing (eg France, Germany, Netherlands)**

Ex officio licensing is a statutory institution whereby a Minister of Health (or like) may grant a licence to use a patented invention for important public health reasons and the parties have not reached a mutual agreement. Such legislation is in force at least in France and the Netherlands. In Belgium, the model of the compulsory licence for public health is reminiscent of the French example, but this licence cannot be triggered by the Minister – only by a third party.⁴²

Licences of right

Some countries (eg Germany, France, and United Kingdom) have adopted a system whereby a patent holder may state officially that anyone may, as of right, have a licence under his patent upon reasonable terms, which will be set by a patent office or the courts if parties cannot agree. The licensee gets a non-exclusive right to use the invention. In return, the patent holder may halve his costs to maintain the patent in force. This system has also been proposed for the Community Patent.¹³

Novel approaches

Clearinghouse model

In a clearing house, all the important patents are collected by a specific organisation that gives access to them against a fee. Some say that it would be almost impossible to know what is in there. Others argue that for gene patents a real clearinghouse model should be developed. It should not just be copied from information technology but adopted to best suit the purpose, and it could be split into several research topics, such as cancer, cardiovascular diseases, and so forth.

Several clearing house models have been presented:^{60,64}

(1) the information clearing house provides a mechanism for exchanging technical information and/or information related to IP status of said information. Examples include patent search sites or platforms. (2) The technology exchange clearing house model provides the list for available technologies for further negotiations, and may also assist in mediating and managing services. (3) The royalty collection clearing house model settles the payments of the licence fees. (4) The open source clearing house model fosters the free exchange of technology. The

genetic clearing house could be a derivative of these. Regional clearing houses could be coordinated globally.⁶⁰ Examples (2) and (3) would be particularly useful for addressing issue 5.4, when it is not *a priori* clear which IPs will be used. The fee structure used by ASCAP (American Society of Composers and Performers), example of (3) should be considered. Successful examples of (2) are publicly funded.⁶⁵

The Nuffield Council⁵ and HUGO⁵³ support the further exploration of the clearing house model proposed by OECD in 2002²⁶ to ease the obtaining of licences for genetic inventions by commercial laboratories and to expedite the rapid and low cost licensing of patented DNA sequences, which have potential applications in clinical diagnosis. This model is said to work where companies need licences to produce electronic equipment meeting international standards, but it is questionable whether it could work in the biotech field, where there are many different players with different business goals.

Centralised databank

An approach, rather similar to aforementioned clearing house (information or even technology exchanging) is the model of a centralised database, like in the United States.⁶⁶ The basic concept of a (National) Biotechnology Database is to bring together the information that prospective licensee and licensors need to enter into efficient transactions. In the database, technology should be described, related IPR listed and information about the prices and licence terms made available. In this model, the participants would act separately, compared to patent-pool or clearinghouse models. Therefore, the problem of patent thickets would not be resolved. This approach forces transparency of the licensing market to lower transaction costs. According to this model, those who wish to participate should disclose their invention, which requirement would not add anything new to current disclosure obligation under patent laws. The transaction cost would be settled among the parties, but the participant would not be obliged to license. Prospective users of listed technologies would only need to consult one source. Venture capitalists might find it easier to value IPR assets traded on a central market.

The NAS has recommended that the Protein Data Bank (PDB) should collaborate with USPTO, the EPO and JPO to establish mechanisms for the efficient transfer of structural biology data in published patent applications and issued patents for the benefit of scientific community.³

Patent-pools

In a patent-pool two or more parties have their patents licensed to a third party separately or in a package which makes it easier to exploit the technology.^{60,67} Patent pools could promote complementary technology and reduce

transaction costs by mitigating the problem of patent thickets.⁶⁸

On the other hand, the patent-pool is said not to work in practice. Small percentages to be paid for many will accumulate to become a big portion, mitigating the own investment. When both big and small companies are involved, division of benefits is complicated. In general, heterogeneity of membership (size, research only or manufacturing, multiproduct or not, and so forth) lead to instability. Study of successful pools (in electronics) suggest although complicated, successful division can be implemented.^{69,70}

A Swiss survey reported that many biotechnology entities were cautious about collaborating with competitors and therefore reluctant to adopt this approach.⁷¹ Furthermore, many did not know how to use patent-pools. The report had found the participation of non-profit research institutes in the pool useful as they balanced commercial interests of the companies.⁷¹

Ebersole *et al*⁶⁷ consider the field of diagnostics a particularly good field for patent pools, because it is commercially focused, and when they are limited to individual diseases, such as breast cancer and cystic fibrosis, and to other diseases for which there is a (international) consensus about which genes and/or mutations have to be tested. In addition, they argue, unlike genomics industry, the parties have a clear common goal: to provide accurate tests and analytical devices so as to minimise false-negative or false-positive results for a given disease. The number of patent holders is expected to be manageable. Moreover, the genetic diagnostics is not anticipated to develop so fast as to not be able to keep track of newcomers to the market, and following this could be a task of the pool's expert committee. A patent pool is according to Ebersole *et al*⁶⁷ usually most suitable for diseases that are detected by multiple genetic variations on either a single gene or for example, polygenic diseases, such as Alzheimer's, cystic fibrosis, spinocerebellar ataxia, myotonic dystrophy, hereditary ovarian or breast cancer, and hereditary haemochromatosis. Instead, diseases caused by a single nucleotide change are often owned by only one or two patent holders, and hence not so likely participant to the pool.

Patent-pools might constitute a cartel and have anti-competitive effects,^{60,67} present the US Antitrust Guidelines of Intellectual Property which have a special section on patent-pools and cross licensing, and which suggest criteria to be used when evaluating the pro/anticompetitive nature of the patent-pools. Important criteria include, inter alia, evaluation of whether the patents are (i) complementary, that is, that can be used together, and are not substitutes, (ii) competing, that is, are substitutes, (iii) blocking, that is, cannot be used without infringing the basic patent; and (iv) essential, that is, have no technical alternative and are useful only when pooled with other.

A purpose-bound patent

As described above, the classical model of patent claim enables the first inventor of a certain sequence to claim an invention which also covers possible future uses of that sequence. Purpose-bound patents could be taken into consideration as a measure against 'over-rewarding' the first inventor and against speculative patents. A purpose-bound patent would restrict the patent so that only specific use disclosed in the patent claim could be granted. Optionally, if the purpose of a DNA sequence is not comprised by the claim, then the purpose (including the function of the protein) could be demanded to be clearly disclosed in the description at the date of filing. Among others, a European Commission's Expert Group⁷² has addressed the scope of patents on gene sequences. A majority of the group did not find objective reasons to construct such a novel regime in the field of biotechnology. The Swedish governmental committee came to similar conclusion, although there were dissenting opinions as well.⁷³ However, different national approaches have been chosen, and for example, France and Germany have implemented the Biotech Directive into their laws in a way which limits the scope of a patent to the purpose(s) disclosed in the claim. The English doctrine of sufficiency is also interesting in this respect. In addition, the Swiss parliament will decide in 2007 about the planned revision of the patent law. This revision contains, *inter alia*, that naturally occurring gene sequences will not be patentable, whereas in the case of derived sequences, the function of this sequence must be concretely disclosed at the filing date (see Appendix A of the Swiss proposal). The European Commission decided in 2005 not to take a position on the validity of these different national approaches due to the different contravening arguments and the current uncertainty relating to the economic consequences of respective laws (Commission report 2005/312).

Open source

Open source approach in the information technology world means that while acquiring a certain software product one also gets the source code and can further own inventions and information technology by using this software without fear of reach-through claims. This approach has not been considered feasible in biotechnology, because the scientific community is driven by much more complex incentives and strategic behaviour.⁶⁰ Furthermore, biotechnological research has partly been funded by venture capital which expects rapid returns. This is particularly true in the United States.

Open is not the same as free. The point in openness is that the data is accessible even though against a fee, whereas business secrets remain hidden in the small circle. The restrictive licensing strategy may hence violate openness if the data is not accessible.

Knowledge sharing is considered to serve the best interests of all science, both basic and applied. For instance, United States science is said to have flourished because of its tradition of general openness and the sharing of data and research resources.³

Voluntary (research) licences in special cases

Voluntary research licensing, that is, the option for a patent holder to explicitly allow research on/with his patented innovation, belongs to one of the many proposals to ease the concerns. However, the downside of initiating a discussion about research licences may be that it indicates a need for a licence in a situation which could normally be covered by research exemption.

Nevertheless, different terms for basic research and commercial use are used in practice. PCR, a fundamental research tool in molecular biology, is a good example. Competing companies have to pay rather high fees whereas, for instance, the Human Genome Project has been said to have access to it on generous terms.⁶⁶

Academia could benefit from campus licences on favourable terms similar to ordinary software licences negotiated centrally in the universities.

In health care crisis or emergencies, patent owners and licensees might decide to contribute without a financial return on a voluntary basis.

Diagnostic exemptions

Clinical use exemption was held as the best remedy regarding patents in a Swiss survey.⁷¹ Clinical use exemption would not necessarily mean the same as gratuitous, but at affordable costs. The distinction between public laboratories and commercial private laboratories may need different treatment.

For instance, a patent covering the BRCA2 gene was granted (in the UK in 1997, by EPO in 2004) to Cancer Research Campaign Technology (CRCT, the commercial subsidiary of the Cancer Research Charity) and its United States partner, Duke University. The Cancer Research Charity gains revenue from the licensing of its patent to commercial organisations, and grants the National Health Services a free licence to perform BRCA2 testing. CRCT offers a free licence to all laboratories working in Europe in non-profit health care.

Price regulatory system as with pharmaceuticals

One solution to control the prices of diagnostic tests would be to develop a similar regulation system than is applied to pharmaceuticals with respect to price regulatory system.

Remuneration-based patent system

The Danish Board of Technology has specifically recommended the establishment of a remuneration-based patent system in which a patent holder cannot prohibit the exploitation of his patent, that is patent no longer provides

exclusivity.⁶¹ The Board suggests that this model would facilitate access to licences, lead to more efficient exploitation of patented knowledge, strengthen patent enforcement and encourage small and medium-sized enterprises, in particular, to acquire patents. Whether these goals would be achieved is thus far questionable.

Genetic sequence right (*Sui Generis* IP Right)

There is a proposal for the creation of the Genetic Sequence Right (GSR) as a *sui generis* system of intellectual property.⁷⁴ The approach resembles open access clearing house (see above section Opposition and Revocation). This section is completely based on Dr Luigi Palombi's contribution to this subject.⁷⁵⁻⁷⁷

A GSR would be administered using the existing administrative system utilised by the present international patent system so as to minimise establishment costs and to facilitate its adoption. A GSR would be granted to the first person to file and disclose a genetic sequence defining genetic material of any origin and explaining its function and utility. A GSR would be the subject of a written application filed in the patent office of the country of application, similar to a PCT application for a patent. The GSR would become part of an international electronic database which would be freely accessible by any person.

Upon registration the GSR holder would have the right to a GSR use fee (GSR fee). The GSR fee would vary depending on the nature of the use. For publicly funded institutions such as universities, experimental use would not attract a GSR fee, but for commercial entities, the GSR fee would apply commensurately with the nature of the use. For example there could be scale for commercial entities starting at experimental use and moving through to full commercialisation. It is envisaged that there would be a multitude of variations in between.

The amount of the GSR fee would be set by a published scale determined by a centralised world body responsible for the global administration of the GSR, for example, The World Intellectual Property Organisation (WIPO). This body would collect and distribute the GSR fee revenue and could earn revenue by the collection of application and annual administrations fees, as well as by retaining a small percentage of the GSR fee revenue collected. Specific allowance could also be made for GSR holders to seek GSR fees above the published scale if the GSR holder could establish that due to factors relating to the nature of the GSR or unforeseeable events (eg war), the total amount of GSR fees would be insufficient to recoup a fair return on the investment in the research and development leading to the GSR.

GSR users would be required to register their use with the local administrative authority and that use would be registered on the GSR electronic database. This would provide a public record of use.

The life of the GSR would be 10 years from the date of registration. Infringement of GSRs could be dealt with through the relevant national courts. The holder would accordingly have the right to seek injunctions, declarations, or damages. Criminal provisions would also make it an offence for breaches of the holder's GSR rights.

Moreover, if the GSR were to be identified through the provision of traditional, tribal or indigenous knowledge or information a portion of the GSR fee due to the GSR holder would be paid to the persons who are the owners of the knowledge or information. Their entitlement would be commensurate with the contribution made in the identification of the GSR and would be determined by the central administrative authority, which would also oversee the distribution of the GSR fee revenue to the relevant peoples.

The GSR would thereby provide a system by which investors in genetic research could be remunerated without the GSR holders having the power to control the uses to which that GSR may be put. The GSR would thereby facilitate the publication of genetic sequence information and encourage the use of genetic sequence information and the production of corresponding biological materials. However, by removing the element of absolute control, the GSR would prevent GSR holders from controlling further downstream research or other uses.

The GSR holder would not need to satisfy any 'invention' or 'inventive step' criteria. Novelty of the genetic sequence could be established by a search of the GSR database or other genetic sequence databases. Novelty of the GSR could also be established by function and utility, so that even if the genetic sequence is already known or the subject of an existing GSR, establishing a novel function and utility not previously known could give rise to a new GSR. However, broad GSR description regarding function and utility would not be permitted unless substantiated throughout the breadth of the description. The GSR would therefore incorporate a description of the function and utility of the GSR.

The GSR would also address the many concerns that surround experimental use (research exemption). For instance, many patents have been granted over 'research tools' that are useful in the search for new drugs. In the context of each of these applications, the patented biological materials have been used by research institutions, such as universities, and the issue that has arisen is whether such use is or should be exempted from patent infringement.

Under the GSR, use by a teaching or research institution would be zero rated for GSR fee purposes. However, a commercial entity's use of a GSR, either directly or indirectly through a university, would attract a GSR fee commensurate with such use. The obligation to pay the GSR fee would remain with the commercial entity. Therefore, if any commercial entity entered an agreement with a university to conduct research on its behalf or as part of a joint enterprise or collaboration, the obligation to pay the

GSR fee would continue. This would remove the debate about when, and if, universities that are conducting commercially funded research should be the subject of a research exemption (see above subpara The most common licensing policies in chapter on licensing).

Balance between competition law and patent rights

Competition policy is directed at improving fair market behaviour. WIPO speaks for a balance to be found between competition policy and patent rights, and this balance must achieve the goal of preventing abuses of patent rights, without annulling the reward provided for by the patent system when appropriately used. In addition to private entities, also public laboratories and public institutions should be aware of potential anti-competitive effects.

The interface between IPR and competition law is a difficult topic. By nature, a patent confers a monopoly. Competition law may be seen as a complementary component to regain the balance to the markets in some cases related to the use of IP rights. However, the use of competition law is not regarded as the prior instrument to amend the problems raised by the patent system.⁶⁸ Some countries have adopted interdisciplinary dialogue between patent and competition fields to foster mutual understanding and to examine how patenting system has caused competition problems. Competition agencies could, according to OECD, publish guidelines telling how they will analyse licensing agreements and other IP-related conduct.⁶⁸

Licensing agreements are usually beneficial to competition because they enable transfer of technology. OECD names two kinds of licence agreements that may be harmful.⁶⁸ First, a 'grant-back provision' obliges the licensee to grant a licence to the licensor on any improvements it has made and patented to the original invention. In particular, exclusive provisions may be harmful in case of significant improvements. Second, a 'patent pool', even though mostly beneficial for competition, may be used as a device for jointly selling what would otherwise be competing technologies, like in the case that the patents are substitutes for each other. In contrast, if the technologies are complementary and essential, there usually are no problems to competition.

OECD has set a principle that licensing practices should not be used to expand the breadth of exclusive rights beyond the scope of the relevant intellectual property rights. Best practice in the field of competition include avoiding unduly restrictive tied-selling, non-compete clauses in areas beyond the scope of licensed genetic invention, and using non-exclusive licence agreements for foundational inventions.¹⁴

EC competition law

Article 81 in the Treaty of Rome prohibits agreements which prevent, restrict or distort competition within the

Common Markets. Exclusive licensing agreements can violate this provision. Article 82 prohibits an abuse of a dominant position. Unreasonable pricing may be used as an example. The Commission has established regulations for specific defined categories of agreement (eg transfer of technology agreements, R&D agreements) that indicate what kind of clauses are prohibited and which are allowed and under which circumstances, so-called block exemptions.

The European Commission has given a decision in 2005 and held that AstraZeneca had abused its dominant position by delaying generic entry by misusing certain procedures, and thus violated the aforementioned Article 82. The company was found to be dominant on the market for drugs used to treat stomach ulcers, and was fined up to 60 Million euros (European Commission, IP/05/737, 15 June 2005).

In the field of patents, especially the Transfer of Technology Block Exemption Regulation and the related (non-binding) Transfer of Technology Guidelines (TTG) are important. The latter are especially important with regard to the assessment of patent pools. The TTG give quite detailed criteria as to the essential character of the patents involved in the pool, the role of a patent expert, and so forth. This is of major importance, as patent pools might cover a cartel or invalid patents.

It is important to know that the United States has asserted jurisdiction also on activities abroad if these activities might adversely affect the foreign trade of their companies.¹³

Societal and economical aspects Biotechnological policies

Biotechnological policies are created at different levels, such as in the EU, Council of Europe, OECD, and United Nations. Policies have partly separated domains, like scientific, environmental, health, market, which have different ideologies. Whether regulation should be based on potential risks rather than demonstrated risks shares opinions. Consequently, the policy-making environment is rather complex.⁷⁸ Denmark issued a very strict law on the use of DNA in 1986, whereas the UK and France promoted self-regulation. Countries slowly adopted their own and often divergent rules, based on different values, which has resulted in a rather fragmented regulation in Europe. This was obvious, for instance, when trying to draft the Biotech Directive.

In 21st century, EU and OECD consider biotechnology a key driver for growth and development in their member countries.^{14,79} A clear enabling environment and regulatory structure is regarded as essential to access the benefits.¹⁴ OECD has had an important role in many fields in creating guidelines and rules that have preceded the national regulation.

UNESCO's International Bioethical Committee, IBC, has also had a norm-setting function in the field of bioethics. In its Report of 2002, it regarded as the basic problem how to secure the benefits of the human genome sequence for the service of the humanity as a whole. It recognised the changes in the tradition of the open science and in the balance of public and private research investments.⁶

Public research institutes and universities

Public research institutions, universities and schools are nowadays directed carefully to protect their knowledge and whenever possible, apply for a patent. Many are worried what that might do to fundamental research that has usually been funded by public money. Commercialisation might have too much directive effect: failings may be hidden, publications are delayed, and research starts focusing on issues that have best potential to become profitable. Cooperation suffers as greed enters into the picture.

Science as a commodity means attempt to secure free flow of information and communication within an academic world.⁸⁰ However, it has been said that the perception of the scientific community as a non-political, fraternal and disinterested is a myth.⁸¹ According to some, biotechnology development is based on rivalry and an important role of venture capitalists.⁶⁶

In the current situation, OECD wants to enhance the situation of academic researchers by paying attention to licensing practices: they should not unduly hinder academic research, possibilities to publish in a timely manner the results of the researcher, and education.¹⁴

The National Institute of Health (NIH) of the United States requires anyone who receives public funding to grant licences freely to other public research institutions.⁸² It has been also insisted that private companies should grant such licences to public research institutions for a nominal licence fee.⁸² A patent is usually a predisposition to the licence negotiations.

The HapMap-project, for instance, prohibits patent claims based on data obtained from its database and requires agreement to a licence agreement from those who want to publish. The deficits of this policy are pragmatic: the policy will not impede patent authorities to grant a patent even though the policy was violated, there is no enforcement mechanism to prohibit the dissemination of such a patent and damages on the basis of contractual breach are speculative.

Reward of joint efforts – co-inventors and other collaborators

History documents many cases where the financial benefit or honour of the invention is enjoyed by someone else than the original inventor, or the other collaborators. For instance, a single researcher may have had an essential input to the invention, but is ignored when applying for a

patent. A right to a patent belongs basically to the inventor(s), but the right can be assigned. Furthermore, often the inventor is obliged to assign the right to the invention on the basis of an employment contract or other agreement, or a local law. The position of co-inventors may also be difficult; because different groups and individuals may have contributed to the development in the long course of time (a good example is the extensive worldwide chase for the BRCA genes, resulting in patents for Myriad Genetics). Public and private institutes and laboratories as well as funders may be involved, who all have divergent expectations of using and sharing the results.

The right to a collection of biological samples is sometimes problematic when many research groups have contributed to the collection of it. Here it is essential to understand that a patent, however, does not focus on a certain existing biological material.

European community

Also the European Commission directs the IPR practices in the member states. It has adopted a strategy to restore European leadership in life sciences and biotechnological research.⁷⁹ Towards this goal, it set the field as the first priority in its Sixth Community Framework Programme for Research (FP6 2002–2006). The Commission expects the Europeans to be the major beneficiaries of biotechnological solutions. Transforming science into applications is essential: besides good technological knowledge, the operators in the field must be able to create new products, processes and services in order to yield a harvest of novel innovations. The Commission has thus set a strict IPR policy to protect and use the knowledge derived from the research it funds, a policy which incidentally has a directive function in terms of patenting activity.

The EU wants to accelerate research and development, as only less than 2% of EC gross national product is currently used for it. While the quality of the European research is considered good, there is a deep concern about the innovation gap between research and production, because this inefficacy may direct big companies to move outside of Europe. The European policy is hence pressing towards enhancing research and development to achieve the 'Lisbon goals', that is, the objective set at the Lisbon Summit in 2000 of becoming the leading knowledge-based economy in the world.

The attractiveness of Europe raises concern. The Austrian and the Finnish Presidencies of the EU arranged a round-table meeting on June 20, 2006 in Helsinki to have a mid-term review of the Life Sciences Strategy.⁷⁹ One of the messages of the meeting was that a new Knowledge Based Approach was hoped for to improve biotechnology in Europe, because Europe is still lagging behind United States and Asia. Several challenges were identified: First, Europe is too fragmented concerning the regulation. Legal certainty is not a reality, and harmonisation of biotechnological

patents has not succeeded. Second, the field does not attract investors any more. Third, to improve public perceptions and transparency of the field, more debate and communication is needed for a successful policy making. The specific theme 'Health' of the Seventh Framework Programme (2007–2013) is, however, expected to improve the competitiveness of European health-related industries. Still, the research activities in Asia may result in surprising patent portfolios.

Legal experts say that too stringent laws operate as disincentive and encourage more investment in the United States (see Mason and Laurie, 2006, p.531).⁴⁵ Comparison between the United States and Europe shows that, to some extent, different patenting criteria between these continents favours patenting in the United States.^{78,83} It has been reported that huge initial development happened in Europe, but that their commercialised action took place in the United States.⁸⁴

Public health care

Along with the proliferation of new diagnostic genetic tests, the course of interest has shifted from the traditional area of (rare) monogenic diseases to more common diseases, such as cardio-vascular diseases, diabetes, and other diseases, the presentation of which interacts with the environmental and life style factors and a possible genetic predisposition. The public health sector is increasingly involved in bearing the costs of these diseases. The way to translate the genetic knowledge to public health improvement requires still lots of efforts. In contrast, many of the currently known health risks, even if worsened by a possible genetic predisposition, do not require specific genetic testing. Tests are not required for all people, but only for those that can genuinely benefit from it and for whom the tests are particularly helpful (see Chapter diagnostic vs non-diagnostic test results).

Public health care system, social security coverage, insurance, *inter alia*, affect an individual's access to a certain genetic test. Licensing policies will further affect the accessibility, either directly through monopolies, or practically, through increased costs. It has been suggested that the right to health should be considered predominant with respect to IPR (see Lenzerini 2006, p. 334).⁸⁵ This might, however, be devastating for the companies' willingness to invest on new tests and drugs. The EC Expert Group has recommended that national healthcare systems should ensure that genetic testing will be accessible equitably to all who need it. Furthermore, the Group suggested that the European Community should take measures to promote diagnostic testing of rare diseases as a matter of urgency.²³

However, the development of drugs and tests for rare diseases is not profitable for industry. It has been suggested that for such non-profitable areas basic research should be publicly funded, and/or broader patents allowed to interest

companies.¹⁸ See also Report of WHO Commission on Intellectual Property Rights, Innovation and Public Health (2006)⁸⁶ about patenting and alternative funding of drug development.

Priorities in genetic services, as all health services, are currently set at local level within the member states. In many of these countries, the society ought to provide needed services, but it cannot, mainly due to lack of resources. The wealthiest people can afford to consult the private services, but this will increase social inequality. The principle of justice, however, requires that services shall not be rationed on the basis of the ability to pay.⁴⁵ The EC expert group (2004)²³ has recommended that the national healthcare system should ensure that genetic testing will be accessible equitably to all who need it for a medical reason.

Exclusive practice of clinical diagnostics worries the NAS which states that 'the performance of a gene-based clinical test in an academic setting often generates rich databases of newly detected genetic variations that can be correlated with phenotypes of large and heterogeneous patient populations.³ Such admixed medical practice and research provides important new information about the mutational repertory of specific disease-linked genes, as well as the phenotypic correlations that provide new insights into disease mechanisms and identify potential new targets for therapeutic intervention'.

Given the immense flow of novel techniques, they should be carefully assessed to measure their quality and effectiveness before accepting them into clinical use. NAS recommends that genomic and proteomic-based diagnostic tests shall be subject to independent validations; and research exemption shall be established to cover the situation when a patent owner refuses.³ Although such validation would not be patent infringement in Europe, legal changes may be needed in the United States. Furthermore, adaptation of new tests also requires safeguarding appropriate genetic counselling. All this has to be considered when allocating scarce resources. The application of the egalitarian principle, as in Scandinavian countries, leads to distribution of resources strictly according to the need whereas some other countries promote utilitarianism, for example, principle striving at the maximum benefit for all (WMA Medical Ethics Manual 2005, p. 72).⁸⁷

Rewarding the health care innovations *vis-à-vis* possibilities of the public health care to maintain efficient, equal and adequate services constitute difficult weighing and balancing dilemma where health-economical calculations are needed. More personalised medicine through pharmacogenomics is expected to help to allocate the limited resources more effectively.⁸⁸ Some new tests might certainly be expensive, but on the other hand, they may be more efficient economically in the long run compared with a conservative treatment that is performed in the lack of accurate diagnosis and potential cure.

Public health is expected to benefit from the genomic knowledge of disease mechanisms, as it could develop strategies to prevention and early diagnosis, such as screening. However, it is doubtful how much people can be motivated really to change their living habits even if they know about the risks. The continuous increase of alcohol consumption and obesity indicate that such a task is not easy.

One of the problems is that patent issues tend to belong to the competence of market government and thus the Ministry of Trade and/or Industry, whereas the consequences are detected in the field of the Ministry of Social and Health Affairs. Same controversy has appeared also at the Commission between different Directorate Generals. More co-operations between sectors are hence needed to have a balanced perception of the effects of the patents.

Patients' interests

Patients are nowadays often enlightened consumers who are informed of their conditions and possibilities. Patient groups are organised to inform the patients and their relatives and also advocate their interests to politicians. Patients do not want to wait long time before performance of the test.²

Accurate health information in an apt manner is essential for the patients. Often, the test result gives something positive to the patients and family. A diagnostic test that is able to verify the suspected diagnosis clarifies the situation in the family and, simultaneously, gives a tool for prenatal or carrier testing in the family. If the test was performed for prenatal or predictive purposes, most results are 'negative' and relieve the fear of the disease. Here, the major benefit is not money, but the life quality. If the test detects a disease or shows that a person is at risk, he or she can be given appropriate genetic counselling and proper treatment, if such is available.

Economic drivers of the companies

No pain, no gain: research and development is risky and often requires capital funding. Many biotechnological companies operate on risk money from capital funders who, in turn, expect results. Biotechnological industry is challenged by mergers, joint ventures, selling of product at an early state of development (prior to clinical trials), countless dead-ends, draw-backs etc. Business is elementary for developing solutions that would benefit members of society, as public funding does not have means to attend to risky pharmaceutical business. Consequently, companies need patents for their IPR portfolios to attract investors.

Hence, one of the advantages of the patent system is that inventors, and subsequently companies that develop the invention into a working product, are able to get a return on their investment because they get a time-limited right

to prevent competitors from entering the market with the invention.

Albeit disadvantages to the practice of the genetic testing as described above, it also benefits of the patent system. For instance, was there a serious limitation to get a return on the investment, companies might draw themselves from this field. Costs involved with the development of the diagnostic test, the standardisation, the quality control, the marketing and the potential liability claims for a wrong diagnosis are not to be taken lightly. Moreover, the developed test will have to compete with the existing tests and must be priced competitively, particularly in the light of the current pressure for cost reductions. Without knowing in advance whether the competitors can be prevented from taking advantage of the investments made by the inventors or the subsequent developing company, it is likely that the latter will be hesitant to invest on the activities mentioned above.

It is possible that companies will occasionally still develop diagnostic tests without adequate patent protection, for example, if another competitive advantage can be exploited. However, rare or rarer diseases that are currently already difficult to support, might not be picked up.

When companies are excluded from entering into the market it is up to other institutions and organisations to address the needs of the field. Where companies have a deep interest in developing the market and obtaining a maximum market development as quickly as possible, it is likely that in general the regionally oriented institutions and organisations have other priorities. It is therefore likely that genetic tests will at least unfold the market at a slower rate than possible when companies are excluded.

On the other hand some companies, albeit relatively few, seem to use their right to exclude competitors to an extent that unfair advantage is obtained. Some companies use patents as strategic tools: they apply defensive patent policy and they want to control the technology.

However, this problem is in fact a problem with the licensing strategy of such companies. Companies that maintain a very strict licensing policy usually invite third parties to attack the underlying patents (see eg BRCA1 example in 2.6). Unless the underlying patents are very strong this potential for attack typically prevents sensible companies from over-exploiting their monopoly. Third parties usually weigh the costs of a licence and the costs of legal action against the chance of success.

Some information about the competitiveness of the genetic diagnostics industry is probably warranted. It is anticipated that the pricing practices are very different to the pharma sector, particularly because they do not have the advantage of 'blockbuster products', whereby one product offsets losses or low margins on many other products. They also disagree with the assertion that it is difficult to invent around gene diagnostic tests, and argue that for a variety of reasons very little reliance is put on

DNA sequence patents (ie Myriad Genetics was the exception, not the rule). In fact, far from patents being a big boon to their business, they argue that the lack of IP protection is one reason why they will not invest in work to prove or improve the clinical utility of their products (K Liddell, personal communication).

'One firm's research tool is another firm's end product'.⁸⁹ Companies that sell small molecule drugs are willing to dedicate new DNA sequences to public, while DNA-sequencing companies regard them as proprietary resources. Downstream patents tend to motivate for research and development, whereas upstream patents make research and development more costly. Companies are generally not willing to invest in research that would only lead to dependent patents.

Instead of applying a strict monopoly strategy, a more active policy in negotiating non-exclusive licences could *de facto* increase the income of the patent holder (eg Cohen-Boyer technology for recombinant DNA).

Jensen and Murray, in 2005,¹ studied human protein-encoding nucleotide sequences and concluded that 20% of these (4382 out of 23688) are claimed as US intellectual property (IP); more than half of these were assigned to private companies.

A company's effective IPR tool may be composed of several elements including more than patents. Some companies rely on trade secrets to defend their inventions. This approach has been supported by some academic researchers, but requires strict non-disclosure agreements (NDA) with penalty clauses and surveillance. Nevertheless, this approach may limit the dissemination of new technology. Upon some estimates, private industry retains some portion of its protein structure information in proprietary databases and hinders access from basic and applied research in structural biology.³ The grace period applied in the United States has been suggested to be adopted in Europe as well accelerate dissemination of inventions.¹⁸

It has been suggested that the industry should establish practices to reflect and alleviate some real problems related to patents and their licensing policies, and also the negative attitudes of the public.^{18,62}

Public perception

It has been reported that in the public opinion there is more concern about the possible applications of patents rather about patents themselves. The study of Human Genetics Commission (HGC) in the United Kingdom showed that one-third of people surveyed even regarded genetics research in itself as unethical interference with nature.⁹⁰ In general, the public attitude is negative towards genetic enhancement, but positive with regard to therapeutic purposes (Danish Council 2004, Workshop 4).¹⁸ So it is not easy to determine the public attitude to issues like granting of patents vs its appreciation of the effect of gene

patents. Nevertheless, it is very important to develop methods making it possible to measure public attitudes to patent human genes.

Debates about biotechnology relate to debates about capitalism and trust in industry, science and politicians. Because the public tends to confuse different aspects of biotechnology, more open discussion and information should be provided by companies. They could, for instance, create dialogue with the society on the use of human genes and utility of patenting, as well as issue clear ethical guidelines to present themselves as trustworthy social players.¹⁸ It is of the utmost importance to maintain or even increase the patients' affirmative position on participation in medical research. Obvious damage to public perception is often caused by the scandalous reporting style of the media. A few bad stories or illustrations get far more coverage than the hundreds of true statements by the industry.

The recent Eurobarometer (published on June 19, 2006) indicated widespread support for European biotechnology. It showed that 52% of those surveyed believed that biotechnology will improve the quality of life. Approximately one-fourth could not decide and only 12% did not believe biotechnology could improve their lives. The results indicate rather widespread support in the member states. For instance, 58% supported the use of their genetic data for health research.

Finding a balance

It has been questioned whether it is in the public's interest to maintain the system whereby private companies have an exclusive right to exploit medically significant genetic discoveries.⁵ Granting of patents may be unethical if inventors get a reward that is not commensurate with their contribution, or if the return to society is not commensurate with the benefit of the patent holder.

When development of a diagnostic test has required significant efforts to convert the basic knowledge of genetic structure into a clinically applicable, reliable test, the need for some incentive is justified.^{3,5} Also development of tests to detect genetic background of common complex diseases should be encouraged, for which the patent system might be an incentive. In other areas of diagnostic testing, broad protection by patents has not been shown to be vital (Nuffield Council 2002, p. 51).³ It should be noticed that development of diagnostic tests usually require significantly lower costs of research and development, and shorter periods of time compared to many steps required before escorting a pharmaceutical product onto the market, conditions under which Aoki and Nagaoka⁷⁰ suggest to aggressively consider utility requirement against granting a patent.

With respect to the whole patent system, a proper balance should be maintained between the effect of a patent right and the contribution thereto, that is, between

private and public interests, since overly broad claims might jeopardise the system instead of supporting it.^{5,18,83} There does not seem to be a common definition of broad patents, nor a holistic understanding of their effects on the society, because in some cases the breadth of a patent may also be justifiable.¹⁸ Aoki and Small have demonstrated how broad patents might be used in case of general essential facility.⁹¹ There seems to be consensus, however, that in case of broad patents, the input to the invention and the exclusive right to assert it should be balanced, and a compulsory licensing system should operate as a safety valve.^{15,18}

Development of new tests may bring along cheaper, easier, faster and more reliable methods, and improve life quality, treatment options, etc. Therefore, before being frightened by the higher licence fees, a thorough health-economics assessment might be beneficial to consider all these aspects.

Knowledge sharing and cooperation are, according to UNESCO, the global interests and the cornerstone of the development of knowledge societies. UNESCO promotes an equal and universal access to information and knowledge, for the progress of science and the generalisation of education.⁴⁴ The Millennium Development Goals adopted by the UN in 2000 also encourage transfer of technology (United Nations 2000).⁹²

The demand for free access to genetic knowledge is expressed by international organisations (eg HUGO, UNESCO, see also benefit sharing above). Free does not necessarily mean the same as gratuitous; for instance, OECD wants to promote access on reasonable licence terms.¹⁴ The main idea is that benefits from genetic research shall be available to everybody.

Improving new negotiation and transaction models for biotechnological inventions

Negotiations between industry, labs, academia and society might have led to new ways of identifying their respective problems and needs. Licensing strategies should be negotiated to respond to the resources at various levels. For instance, there could be different standards for basic and/or public research, therapies, diagnostics, and so forth. The counterargument is that the public sector constitutes a major economic playfield for medicinal products and technologies.

Governments might have a more active role in ensuring that, for instance, public hospitals have access to necessary diagnostic tools and that they do not violate patent rights. Large university hospital units could join their forces and acquire campus licences to the most relevant research tools. Already, some units in hospitals take care of certain common acquisitions, like machines, technical tools, general software, and the like. For this, the acquisition units must basically follow the competitive bidding

regulations. This works naturally only if there are competing products, which is often not the case in diagnostics.

Self-regulation

The OECD report summarised in 2002 that experts were reserved about suggesting changes to existing patent laws.²⁶ Instead, they encouraged administrative and other regulatory approaches, such as developing a code of conduct, with respect to patents (eg examination procedures) and licences (best practice guidelines, compulsory licences, OECD 2002 p. 82).²⁶ Industry could also take this initiative. Self-regulation is often an efficient and flexible mechanism in special fields, and better adapted among its members than any up-down regulation.

Education and corporate governance

Academic institutions should ensure that researchers and students understand their responsibilities and obligations regarding different laws and agreements. Corporate governance should also be established in the public health sector. Currently, the wrong people try to manage with all kinds of legal and administrative issues. Furthermore, the legislative responsibility in IPR issues is, in many countries, in the Ministry of Trade and Industry or some other cabinet not well prepared to handle public health aspects.

The medical community lacks a holistic perspective to decide which genes can be and are patented, for what functions they are patented, and when will they expire. For this, an expert would have to read and understand all patent claims to know the scope of the patent, which is currently rather unrealistic, even though good databases exist.

The OECD encourages specific training programs on IPR issues.¹⁴ The EU has also included educational goals in the life science section of its strategy.⁷⁹

Future research needs

Existing studies are not regarded as sufficient to establish whether patents in the biotech pose a problem or not to the research or the availability of the novel technologies;^{7,27} what is the frequency of harmful licensing practices; what is the true frequency of accumulated licence fees? Or is just general dislike against the idea of paying fees to use genetic knowledge? The actual impact of patenting and licensing practices on industry and public research should be studied.²⁶

Future research needs to include the examination of whether current practices in patent examination have allowed multiple conflicting patents on the same gene; the scope and importance of the anticommons problem;²⁷ and the impact of research tool patents on biomedical research.⁵⁶ An external examination of gene patents is, however, reported to be extremely difficult.^{11,15}

Conclusions

The purpose of this ESHG project was to highlight the problems, gather information from the different stakeholders and to have an open discussion. This goal has been achieved, even though the problems have not been solved. Controversy still aroused surrounding the issue of whether genes and genomic information should be patentable or not. This study indicates that there are real concerns that need to be taken seriously. The current, unresolved situation is intolerable as clinical and research professionals are uncertain of their freedom to operate.

A limitation of this consultation process is that, in view of the current legal framework in Europe (with the EPC and the Biotech Directive 98/44), it may be difficult for the current policies to be revisited. However, the fact that some member states have been reluctant to transform the Biotech Directive into their national laws indicates that gene patenting is not readily accepted in Europe. Hence, Europe should remain open to the possibility of reopening the discussion on the patenting of genes and genomic data, especially when the debate has not been resolved at an international level.

Many opinions have highlighted the need to retain the possibility of patents, because otherwise there would not be incentives for the industry to develop new tests and treatments. Others, however, strongly question gene patents and fail to see the importance of patents to the innovation.

It is possible that the problems faced today may stem from earlier practices. Certain problems seem to relate to the examination in the patent offices. Some commentators indicated that there is an absence of any real check and balance in the patent system and that the patent offices are currently unable to properly vet patent applications. There is currently also a backlog in the patent offices, that is, there is a huge amount of patent filings under examination.

One fundamental concern has been the breadth of the genetic patents. Many of the workshop participants and contributors felt that the establishment of a link between a disease and a genetic sequence or a defect should not be patentable due to the lack of inventive step and the lack of novelty. Furthermore, in their opinion, individual mutations in known disease genes should not be patentable either. Indeed, restricting the granting of a patent to a specific purpose might be necessary because many questions relating to genetic functioning and interactions are still unknown.

Totally new problems may be developing along with all the new techniques and 'omics': there is a gradual shift from gene-based tests to genome-based tests, and, for instance, a combination of metabolic and molecular biology. Genome-based diagnostics and multiple gene tests may create new challenges in the field. Recent news tells us that patent claims for RNA interference are emerging and might bring along serious patent thickets.¹⁷

Clinical utility can be shown only after years on the market. This should not be left to a limited party. Rather there should remain space to develop the patented invention further in the scientific community. This is particularly important with respect to diagnostic, prognostic, therapeutic and preventive developments for multifactorial diseases, which are anticipated to replace rare monogenic diseases in patent applications.

How does one predict which of the pending patent claims are to survive? Some experts proposed economic disincentives such as penalties and damages against patent holders that seek and enforce invalid patents. The mere grant of a patent is no guarantee of validity. Patentees are in the best position to know about the validity of a granted patent and so if a court finds that the patent is invalid, those adversely affected by the patent-holders' prior actions should be compensated by the patent holder. This type of disincentive would provide a check and balance against overreaching of broad patent claims. Strong requirement for utility should reduce patents on very basic technologies and is expected to give incentive to find utility.

The court system is reliant upon litigants challenging the validity of patents. But the litigation is expensive, takes a lot of time and the outcome is unpredictable. Therefore, there seems to be pressure for governments to introduce an intermediate body that scrutinises patents and challenges them in appropriate circumstances.

Many of the concerns seem to relate to licensing but their real effects and availability are so far unclear. Albeit some examples of exclusive licensing policies, as was attempted in the BRCA case, these seem to be an exception rather than a rule and a real threat. Instead, the magnitude of many patents relevant for the use of a certain product or process appears to pose a difficult dilemma. On the other hand, there may be a tragedy of anticommons: nobody or only few use the invention(s) or patent(s) due to high accumulated fees. One practical problem is that the clinicians, clinical laboratories and researchers do not know who the patent holders are and which methods are covered by a patent.

Licensing strategies should be negotiated to respond to the needs and resources at various levels. For instance, there could be different standards for basic research, therapies and diagnostics and so forth. Governments should be more active in this respect. They should secure that hospitals have access to necessary diagnostic tools and that they do not violate patent rights. There could be professionals in the hospitals responsible for diagnostic technologies similarly to certain other acquisitions, such as machines, technical tools, general software, and so on. Ideally, the licence fees should be reasonable, because high licence fees lead to disapproval and accusations of licensing as a whole, even though there probably is no better alternative. Would the final outcome still prove to be more economical by paying the licence, all things considered?

Benefit sharing ideology is largely supported by the global community of policy makers (see Morality and order public clauses in the legal instruments and some court cases). Concrete ideas of how to introduce this idea in the field of patents are needed.

As presented above there may be different (old) remedies and novel approaches to the problems and concerns indicated in this background document. The most radical solutions proposed include a shift away from the patent system and the replacement of it with a *sui generis* right that is more equitable. Many others think that the traditional patent system functions rather well and serves the interests of the society to an adequate sufficiency. Either way, the active application of these measures is worth considering and needs concrete initiatives from the different stakeholders.

But are we now approaching the end of era of gene patents, as some predict?⁴ Or are the patents just changing by nature? Because the ESHG cannot act as an oracle of the future, at best it can react here and now to the current situation and take part in the challenging discussions on the genetic patents with a special focus on diagnostics.

Disclaimer

The views expressed in this study do not necessarily reflect those of the individual authors and experts, and their institutions.

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Abbreviations

COE	Council of Europe	OECD	Organisation for Economic Co-operation and Development
EGE	European Group on Ethics in Science and New Technologies	PCT	Patent Co-operation Treaty
EPC	European Patent Convention	R & D	Research and development
EPO	European Patent Office	SNPs	Single nucleotide polymorphisms
EST	Expressed sequence tag	TRIPs	Trade-Related aspects of Intellectual Property Rights
HGC	Human Genetics Commission (UK)	UNESCO	United Nations Educational, Scientific and Cultural Organization
HUGO	Human Genome Organisation	USPTO	United States Patent and Trademark Office
IBC	International Bioethics Committee (UNESCO)	WHO	World Health Organization
IP(R)	Intellectual Property (Rights)	WIPO	World Intellectual Property Organization
JPO	Japan Patent Office	WTO	World Trade Organization
NAS	National Academy of Sciences		
NIH	National Institutes of Health		

Glossary

Biological material	Any material containing genetic information and capable of reproducing itself or being reproduced in a biological system (Biotech Dir).	Clinical utility	Benefits and risks of the positive and negative results of the test. Test should be considered only if benefits outweigh harm (Ibarreta D, Bock A-K, Klein C, Rodriguez Cerezo E: Towards quality assurance and harmonisation of genetic testing services in the EU. IPTS – Institute of Prospective Technological Studies, Publ. EUR 20977, 2003, p 39).
Blocking patents	Defensive patent; a patent which does not cover what the patentee is doing, but which he hopes will keep competitors away from his area of interest (Grubb PW: Patents for Chemicals, Pharmaceuticals and Biotechnology. 4th ed. Oxford University Press, 2004).	Clinical validity	Clinical sensitivity (positive in the affected) and specificity (negative in the controls), that is, accuracy with which the test predicts the presence or absence of a clinical condition or predisposition (Ibarreta D, Bock
Claim	The part of the patent specification, which defines the scope of protection.		

	A-K, Klein C, Rodriguez Cerezo E: Towards quality assurance and harmonisation of genetic testing services in the EU. IPTS – Institute of Prospective Technological Studies, Publ. EUR 20977, 2003, p.39).	technology: multiple licences are needed to use the technology.
Compulsory licence	A licence which government authorities or courts force the patentee to grant another party.	Prior art All public knowledge before the priority day relating to the invention level of science when filing a patent.
Dependent claim	A claim incorporating all the features of an earlier claim to which it refers.	Reach-through claim In a patent for an assay or screening method, a claim to any compound found using the method, that is, claims to future inventions based on currently disclosed inventions.
Microbiological process	Any process involving or performed upon or resulting in microbiological material.	Reach-through royalties Royalties paid on the sales of a drug found using a screening method covered by a patent, with or without reach-through claims.
Ordre public	An old legal concept adopted particularly in Constitutional Law, which refers to the conditions under which a democratic state can limit the liberty of its citizens (MONTESQUIEU 1758: De l'Esprit des lois, Livre XI, Chapitre II-III, p. 324 Editions Gallimard 1995). There is no exact definition, but for instance, the French Constitutional Court, while not exactly defining the notion of <i>ordre public</i> , has on the basis of its praxis and on its the centennial use in French administrative law stated that <i>ordre public</i> can be understood to include at least the following: good order, security, health and peace, whereas it does not refer to the human dignity, which is stipulated by other provisions (Conseil constitutionnel: Libertés et ordre public. 2003 (France). http://www.conseil-constitutionnel.fr/dossier/quarante/notes/libpub.htm).	Research exemption Possibility to use the invention for research purposes without a licence. Narrow interpretation.
Patent-thickets	Overlapping set of patent rights with different patent-holders to certain	Royalty stacking The accumulation of royalties to be paid due to the need to acquire several licences to several patents particularly in case of patent thickets.
		State of the art The total information in the relevant field known to the hypothetical person skilled in the art.
		Transcription The process through which a DNA sequence is enzymatically copied by an RNA polymerase to produce a complementary RNA. Or, in other words, the transfer of genetic information from DNA into RNA. In the case of protein-encoding DNA, transcription is the beginning of the process that ultimately leads to the translation of the genetic code (via the mRNA intermediate) into a functional peptide or protein.

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Appendix A

LEGAL FRAMEWORK

Introduction

The sources of patent law in Europe constitute a multi-dimensional and multilevel system: International, European and national provisions affect the legal status of patents in Europe. The EC Directive 98/44/EC on the legal protection of biotechnological inventions (later referred to as 'Biotech Directive') aimed at harmonising patentability criteria for biotechnological inventions. However, it did not create any new patent authority or mechanism for patent application. Therefore, the EPC and national laws constitute the core regulation on patenting. Furthermore, some international agreements oblige the Member States, such as the WTO Agreement on TRIPs of 1994.

Relevant in the field of global patent policies and practices is also the trilateral co-operation of Japanese,

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European and US patent offices. They have issued several joint reports and comparisons of their respective systems and these can be studied at www.trilateral.net. This indicates an attempt at gradual rapprochement between these regimes which would be most welcomed in the global markets.

European Patent Convention: a European patent

The European Patent Convention of 1973 provides a general legal framework on all kinds of patents, so biotechnological patents are not separately addressed. Currently EPC has 31 members, of which 24 are the EC member states. Other members are Bulgaria, Iceland, Switzerland, Liechtenstein, Monaco, Romania and Turkey. Albania, Bosnia and Herzegovina, Croatia, Former Yugoslav

Republic of Macedonia and Serbia and Montenegro recognise a European patent.

The patent granted by the EPO, is called a European patent. Despite the term 'European patent', it is not an EU institution. The EPO has, however, incorporated the main provisions of the Biotech Directive into the Implementing Regulations of the EPC in 1999.

A European patent is not just one single patent but an institution subject to further regulation of national patent laws. A European patent becomes in force in the nominated states according to respective national patent laws, and may also become subject to national legal actions, such as opposition and revocation procedure. Therefore a patent filed and granted by EPO may de facto be treated differently in different national states in terms of time, restrictions, research exemptions, infringements, and so on. There is, however, an attempt to set up a European Patent Court to remedy this problem. The Contracting States of EPO set up a Working Party on Litigation in 1999 to reflect several aspects of a potential common appeal court for patent litigation. The European Patent Litigation Agreement (EPLA) has been negotiated, but an agreement has not been reached (See EPO: Assessment of the impact of the European patent litigation agreement (EPLA) on litigation of European patents. www.european-patent-office.org). One of the problems is that the European Commission opposes the potential conflicting system with the planned Community Patent system, the appearance of which lies somewhere in the future. The proposal for a European Patent Court is also being opposed by some because the European Patent Office would have the power to appoint and remove judges, as well as, appointing EPO patent examiners as judges. This means that the proposed court will not be independent of the EPO and this is regarded as unacceptable.

The value of the European patent is in the simplified procedure, when one office can do the examination, and by one application the applicant can reach patent protection in several countries. An applicant may nominate in which of the member states it wants the patent protection. A patent applicant may also or instead choose to apply for national patents in national patent offices that are equally enforceable. Some choose to file both the European patent and national patent. National patent offices are not obliged to and do not necessarily even have possibilities to follow EPO practice.

Everybody can communicate with the EPO. Also scientific letters will be considered, even though examiners of EPO are expected to have expertise and follow new technologies. Anyone also has the possibility of following the pending or granted patents in the EPO and start an opposition procedure. The Enlarged Board of Appeal has the final saying about the interpretation of the patent law.

United Nations

World Intellectual Property Organization World Intellectual Property Organization is a specialised agency of the United Nations. WIPO does not grant any patents but aims to simplify the process of patenting: It administers a number of IP-related treaties and systems, which enable users in the member countries to file international applications for patents, international registrations for trademarks, designs, and appellations of origin.

Under *The Patent Co-operation Treaty (PCT) 1978* an applicant wishing patent protection on several countries can file only one patent application in a national patent office (or in WIPO), instead of many applications in each country. An International Searching Authority will carry out a search for prior and preliminary examination. The patent process will be, however, concluded in each country, who will decide about granting or revoking the application. For further information about PCT, see www.wipo.int.

The Paris Convention of 1883, the International Convention for the Protection of Industrial Property, is based on reciprocity: each Member State must apply to nationals of the other member states the same treatment as it gives to its own nationals. A patent application will also receive a right of priority: Within 12 months from the filing date of an earlier application (priority date) filed by a given applicant in one of the member states, the same applicant may apply for a patent in any other member state. These later applications will then enjoy a priority status with respect to all acts accomplished after the priority date which would normally destroy the patentability of his invention.

World Trade Organization: TRIPs Under the Article 27(1) World Trade Organization's (WTO) TRIPs agreement of 1994, patent protection shall be guaranteed to products and applications in all the fields of technology. The Article 27(3) TRIPs, however, states that members may exclude from patentability diagnostic, therapeutic and surgical methods for the treatment of humans and animals.

United Nations Educational, Scientific, and Cultural Organization: International Bioethics Committee Articles 1 and 4 of the United Nations Educational, Scientific, and Cultural Organization's (UNESCO) universal declaration on the human genome and the human rights (1997) state that the human genome is in the symbolic sense the heritage of humanity and it shall not, in its natural state, give rise to financial gains. The concept of natural state has not, however, been able to be defined.

In 2001, the International Bioethics Committee (IBC) (2001) advised the Directorate-General as follows:

- (1) The IBC, after considering this issue, is of the view that there are strong ethical grounds for excluding the human genome from patentability;

- (2) It further recommends that the WTO, in its review of the TRIPS Agreement, clarifies that in accordance with the provision of Article 27(2)1, the human genome is not patentable on the basis of the public interest considerations set out therein, in particular, public order, morality and the protection of human life and health. (Advice of the IBC on the patentability of the human genome. The 8th session of the IBC, Paris 12–14 September 2001)

World Health Organization World Health Organization has in 2003 addressed the issue of patenting and suggested that gene sequences without proven utility should not be granted patents. The WHO also demanded for some return of benefits to those who have contributed, for example, certain family or ethnic group with a particular gene variant on the basis of principle called equity.

European Union

The Biotech Directive and related documents The Biotech Directive's objective has been to harmonise patent legislations in the member states and to clarify situations, such as what is patentable and what is not in the field of biotechnological activity.

The EC member states were obliged to implement the Biotech Directive by the end of July 2000, but the process proved to be difficult in many countries; majority of the old member states implemented it first in 2004. The EPO has applied the Biotech Directive in its practise since 1999.

The Biotech Directive does not intend to affect the basics of patent law, that is, patenting criteria, settlement of infringements, and so on. It does not create authority to grant patents and explicitly states that member states shall protect biotechnological inventions under national patent law.

There are many patents that were applied for and granted prior to the Biotech Directive becoming law in EU member states. These pre-Directive patents are subject to the EPC and national patent laws of the member states as they applied at the time of application and grant. With regard to these patents it is not certain that merely isolating and cloning a gene, even though an artefact or artificial in the isolated state, is patentable subject matter under art. 52.1 EPC. In the UK, for instance, direct support for this view is found in the UK Court of Appeal decision *In Genentechs Patent* (1989) and indirect support in the House of Lords decision in *Kirin Amgen v TKT* (2004).

In the Biotech Directive, 'biological material' means any material containing genetic information and capable of reproducing itself or being reproduced in a biological system. 'Microbiological process' means any process involving or performed upon or resulting in microbiological material. According to the Article 3(1) of the Biotech Directive, inventions which are new, which involve an inventive step and which are susceptible to industrial application shall be

patentable even if they concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used. Article 3(2) states that biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if they previously occurred in nature.

Article 5(1) of the Biotech Directive excludes 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 the gene, from patentable inventions. However, the second paragraph 5.2 highlights the difference accrued by isolation of a body element by technical means. Two requirements that make the situation different between articles 5(1) and 5(2) have been thus inserted: isolation and a technical process, that is, involvement of an inventor. Even so, many people consider these articles are contradictory.

The judgement of the Case C-377/98 (Netherlands vs EU, application in the European Court of Justice for annulment of the Biotech Directive 98/44/EC) is very important with respect to the Biotech Directive and the EC IPR policy. The application included six pleas which were each rejected.

Because of an immense confusion around the Biotech Directive, the Commission has so far initiated two reports:

The Commission Report of 7 October 2002 on the development and implications of patent law in the field of biotechnology and genetic engineering (COM(2002) 545 final – not published in the official journal).

This first report on biotechnology, genetic engineering and patent law (<http://www.eu.int/scadplus/leg/en/lvb/l26026a.htm>) concludes that the European legislator has endeavoured to create a functional system, which respects the ethical principles recognised within the European Community. The Commission also highlights its role in monitoring and assessing scientific and legal developments in the biotechnology sector.

This report was able to identify two key topics:

- (1) the scope to be conferred to patents on sequences or partial sequences of genes isolated from the human body;
- (2) the patentability of human stem cells and of cell lines obtained from them

The Commission Report of 14 July 2005 on the development and implications of patent law in the field of biotechnology and genetic engineering (COM(2005) 312 final – not published in the official journal).

This second report sets out the key events which have occurred since publication of the first report. It focuses on issues in the area of patenting gene sequences which have been isolated from the human body and the patentability of inventions relating to stem cells. It also reports on the implementation of the Directive.

The European Parliament adopted a resolution on patents for biotechnological inventions on 26 October 2006 (P6_TA(2005)0407). It named biotechnology as one of the key technologies for the future and regarded patents as necessary to promote innovation. It urged the importance of the definition of ethically motivated limits. The resolution was preceded by several motions for a resolution (B6-0551/2005 – 0557/2005) representing different views towards gene patents in general. It pointed out that even though the Biotech Directive allows the patenting of human DNA only in connection with a function, it has remained unclear whether a patent on DNA covers only the application of this function or whether other functions are also covered by the patent. In the resolution, the parliament calls on the EPO and the MS to grant patents on human DNA only in connection with a concrete application and for the scope of the patent to be limited to this concrete application so that other users can use and patent the same DNA sequence for other application (purpose-bound protection). The Parliament also regards that patent EP 1257168 violates the Biotech Directive.

One of the targets of the European policy with respect to genetic testing has been expressed in the initiative of the European Parliament (Temporary Committee on Human Genetics and Other New Technologies in Modern Medicine: Report on the ethical, legal, economic and social implications of human genetics November 2001) which states that if the advantages of genetic testing are to be understood, three equally important conditions need to be satisfied:

- (1) reliable tests available on the same basis to all;
- (2) counselling that respects individual freedom;
- (3) technology.

Community Patent Convention: Community Patent

There have long been attempts to achieve a single European patent covering all member states. For this, the Community Patent Convention (CPC) was signed in 1975. Some initial proposals for process were found implausible by many and thus the process has been delayed. The Community Patent (CP) would still be granted by EPO, but instead of the national courts, the questions of validity and infringement would in the future be handled by a new institution, the Community Patent Court.

Intergovernmental Organisations

Organisation for Economic Co-operation and Development Organisation for Economic Co-operation and Development has been actively involved in the field of biotechnologies and has issued many policies, such as the very recent Guidelines for the licensing of genetic inventions in 2006. In 2002, it issued a thorough assessment of the impact of patents on genetic inventions called 'Genetic Inventions, Intellectual Property Rights and Licensing

Practices. Evidence and Policies', including suggestions presented in an adjoining workshop.

Council of Europe The Council of Europe has for a long time given recommendations and taken initiatives for international conventions on important bioethical topics through the CDBI. One of the most significant is the Biomedical Convention of 1997 even though not so many European countries have ratified it yet. For instance, UK, Belgium, Germany and Spain have not even signed the document.

National Legislation and Recommendations of National Councils

Currently all the EC member states are also part of the EPC and the TRIPS and should have implemented these instruments and the Biotech Directive to their national laws. Nevertheless, these instruments have left space for national particularities, and therefore there is a need to know some basic differences in different countries.

Some national legislations are briefly presented in the following:

Austria Austrian patent law (BGBl. I Nr. 42/2005) allows the use of a patented invention for research purposes. The Biotech Directive was transposed in 2005 in conformity with it. The Bioethics Commission gave in 2002 its opinion on the national implementation of the Biotech Directive. It regarded the implementation as a positive development from the ethical point of view, but highlighted that it is only a milestone and does not cover or clarify all the issues.

Belgium The Belgian Patent Act is from 1984. The Biotech Directive was implemented in 2005 rather literally (The transposition law on 28 April 2005. – Loi modifiant la loi du 28 mars 1984 sur les brevets d'invention, en ce qui concerne la brevetabilité des inventions biotechnologiques <http://www.ejustice.just.fgov.be/cgi/welcome.pl>). The Belgian Patent Law contains, however, some deviating provisions: a stringent requirement with respect to industrial application of a sequence or a partial sequence of a gene: the industrial application shall be concretely disposed in the patent claim (Art. 4 of the patent law). Furthermore, the transposition law extended the research exemption to cover acts performed on scientific purposes on and/or with (*sur et/ou avec*) the patented invention (Art. 28 section 1er (b) of the patent law). In addition, the transposition law inserted a new article 31 (bis) to the patent law pertaining to the compulsory licensing for the public health interests.

Denmark Denmark transposed the Biotech Directive to its Patent Law (479/1967) in 2000. The transposition law (412/2000) followed closely the Biotech Directive. However, there has been a discussion about biotechnological patents. The Danish Council arranged a conference on the

ethics of patenting human genes and stem cells in 2004. Subsequent conference report and summaries listed key areas and the Danish Council of Ethics gave recommendations (www.etiskraad.dk).

Estonia Patents Act of 1994, amended in 1999 to transpose the Biotech Directive as of January 1, 2000. Private and non-commercial use of the patent is not considered to infringe the patent right unless it infringes the interests of the patentee (Art. 16). Compulsory licensing provisions (Art. 47) cover various situations in the interests of promoting development and Estonian economy. The Estonian patent law requires a registration of voluntary licences to have certainty to a third party (Art. 46 (4)).

Finland Finnish Patent Act of 1967 was altered to transpose the Biotech Directive in 2000 in conformity with the Directive. The Finnish Patent Act does not have a special provision on research exemption. The exclusive right to use the invention does not cover non-professional activities and the research on the invention (Art. 3 section 3). However, non-professional use has been interpreted very narrowly: non-commercial end of the activity alone does not allow the use of the patented invention. In the legal doctrine, only personal and other purely private use has been regarded as non-commercial. Hence, diverse research activities in the universities, *inter alia*, may infringe the patent. It is noteworthy; nevertheless that only intentional infringement may be subject to a penalty whereas mere negligence may lead to liability to pay damages (Art. 58 section 1). In the case of pure ignorance, the infringer may be condemned to compensate the use of the patented invention to the amount that the court finds reasonable (Art. 58 section 2). It is finally for the prosecutor or the plaintiff to prove the decree of negligence. Liability under criminal code (1889) requires intentionality and remarkable economical damage.

France The French regulation of patents is in the 'Code de la propriété intellectuelle, Livre VI'. French patent provisions include institutes such as licences of rights (Art. L 613-10) and *ex officio* licensing (Art. L 613-16). France transposed the Biotech Directive in 2004 (Loi no 2004-1338 du 9/12/2004) (www.legifrance.gouv.fr).

The French National Bioethics Committee CCNE (Comité Consultatif National d'Éthique pour les sciences de la vie et de la santé) has issued an opinion nr 64 in 2000 concerning biotechnological inventions. It concluded that the text of the directive left the situation ambiguous and could not secure the ethical and other interests of the stakeholders. Thus, a debate is needed. CCNE did not suggest that genetics should be excluded from the scope of patent law, but 'the result must not constitute a threat over free access to the field of discovery, a drift in the direction of treating the human body like an instrument, or refusing

to share the benefits expected from these scientific advances'. (www.ccne-ethique.fr).

Germany German National Ethics Council (Nationaler Ethikrat) published an opinion in 2005 of 'the patenting of biotechnological inventions involving the use of biological material of human origin' (www.ethikrat.org). The council favoured transposing the Biotech Directive. It required careful monitoring of further development and of the practice of the patent offices and the courts, in particular, prohibitions on the grant of patents on *ordre public* grounds and handling of the award of the compulsory licences. The criteria applied should be disclosed and clarified in all the relevant cases relating to *ordre public* and compulsory licensing. The Council stated that the compulsory licences should be applied in all suitable cases. Among the specific recommendations the Council suggests that the technical function (industrial applicability) of the invention should be included in the claim. Furthermore, the provision of informed consent should be obligatory.

The German road to transposition was not easy, and was delayed. The main controversy lied on the composition of matter doctrine for DNA-sequences, that is, the absolute protection. There did not seem to be a balance between the society and reward for the inventor. Product patents on human genes and cells were seen as violating human dignity or it was contrary to common heritage of mankind. Furthermore, new findings indicated the number of human genes was significantly lower than first estimated. Also, most diseases are multifactorial. Public attitudes were against Edinburgh patent granted in 2000. Moreover, Germany waited for the ECJ decision on the claim raised by the Netherlands. Later, there was continuing disagreement concerning the Biotech Directive's content and meaning. The hesitation resulted in the conviction of the ECJ in October 28, 2004. Finally, the law transposing the directive came into force on February 28, 2005 (Bundesgesetzblatt January 28, 2005). However, as in France and Luxembourg, Article 1 a section German Patent Law (Patentgesetz) requires that the industrial application of a sequence or a partial sequence of a gene must be concretely disclosed in the patent application by indicating the function. In case the subject matter of the invention is a sequence or a partial sequence of a gene, the composition of which is similar to a naturally presenting gene, then the use of the sequence for which industrial application has been specified in detail, shall be stated in the claim. The explanatory statement rules the prescriptions of Embryo Protection Act shall prevail. Thus, any patents on germ cells or stem cells are excluded in Germany.

Italy The Italian Government issued in January 2006 a decree to implement the Biotech Directive into national legislation (Decreto-Legge 10 gennaio 2006, n.3). The Parliament approved this on 14 February 2006. The main

deviations from the Directive relate to the absolute ban to grant patent protection to certain inventions relating to assisted reproduction. Under Article 4, all uses of human embryos, stem cell lines included, and all techniques using human embryonic cells are excluded from patentability.

The Netherlands Patents are regulated by the Patent Act of 1995 (Rijkssoctrooiwet, <http://wetten.overheid.nl>).

The Netherlands opposed heavily to transposing the Biotech Directive and appealed to the European Court of Justice to invalidate the Directive on several grounds which were all rejected (C-377/98). Finally, it transposed the Directive in 2004.

It has been said that after the adoption of the EPC in 1973, the Dutch patent office had to change its previous very strict examination policy to a policy that is rather loose in practice.¹³

Spain Spain adapted the Biotech Directive in 2002 (Ley 10/2002 de 20 Abril, por la que se Modifica la Ley 11/1986, de 20 Marzo, de Patentes, para la Incorporación al Derecho Español de la Directiva 98/44/CE, Boletín Oficial del Estado', 30/04/2002, No 103, p. 15691). The transposition law followed the Biotech Directive. The Spanish Patent Law provides a list of situations in which an obligatory licence may be granted (Artículo 89). Also, research exemption (Artículo 52) includes many acts that are not considered to infringe the patent, such as, *inter alia*, acts performed in private and non-commercial contexts, experimental uses on the patented invention. In the tenth chapter to the beginning of the transposition law (2002), it has explicitly paid attention to the requirement of the informed consent: while recognising the notion of informed consent, it is not a precondition for patentability, nor a ground for a revocation.

Sweden Sweden implemented the Biotech Directive in May 2004. The Swedish patent law (patentlag 1967:837, <http://rikslex.riksdagen.se>) is consistent with the Directive. The research exemption covers basically only the study of the invention itself. The Swedish Government, however, set up a committee to consider praxis and effects of biotechnological patents. As a priority, the Committee evaluated the issue of the absolute product protection on genetic patents. In a sub report published in 2006 (SOU 2006:70), the committee did not find justifications to change the current system into the purpose-bound patent protection. The final report on several gene patent-related aspects is due in 2008.

Switzerland The 'Loi federal sur les brevets d'inventions' (1954) stipulates the patentability of diverse inventions.

The Swiss biotechnology industry has an interest in conformity of Swiss national regulations with international regulations. This is in particular the case since Switzerland has a long tradition in the pharmaceutical

industry and since Switzerland is the home country of important biotechnology companies. The Swiss regulations has been planned to be adjusted to those of the Biotech Directive. The proposed patent revision is supposed to be discussed in the Parliament in 2007. Under the proposal, Switzerland would not allow the patentability of naturally occurring gene sequences. The protection awarded to claims on derived DNA sequences is limited to those parts of the sequence which fulfil the concretely described function. The list of biotechnical inventions, which are excluded from patentability, will be extended. The compulsory licences are introduced, also to diagnostics (Art. 40 c), as well as the post grant opposition on several grounds like for example ethical principles. Within the revision, it is planned that the opinion of ethics committees can be taken into consideration in the case of an opposition. The National Council approved the law revision on 20 December 2006. It will come in force as later announced. Along with the patent law reform Switzerland is also about to establish a specific federal patent tribunal. For more information on the revision see <http://www.ige.ch/F/jurinfo/j100.shtm#a03>.

United Kingdom The Patents Act 1977 harmonised the British patent law with the EPC. The Biotech Directive was transposed in three stages due to certain constitutional rules governing law making. The articles 1–11 of the Directive were implemented in 2000, article 13 and 14 in 2001 and article 12 in 2002. The patent authority of the United Kingdom is the UK Patent Office (<http://www.patent.gov.uk>). It has issued extensive examination guidelines for patent applications on biotechnical inventions in 2006 (<http://www.ipo.gov.uk/biotech.pdf>). The Courts have applied the patentability criteria stringently and thus the UK has avoided many of the problems met in continental Europe.

An independent UK organisation, the Nuffield Council of Ethics initiated a discussing paper on 'The Ethics of patenting DNA' in 2002. This publication contains also conclusions and recommendations derived from the workshop meetings.

United States of America The US patent policy has differed from that of the European or Japanese. The basic differences have been the United States principles of first-to-invent and 1 year grace-period, lack of opposition-procedure, and lack of provisions of *ordre public* or research exemption.

The USPTO published new Utility Examination Guidelines becoming effective as of 5 January 2001 to be used by office personnel in their review of patent applications for compliance with the utility requirement of 35 USC 101 (US Constitution) (Federal Register/Notices 2001:66(4);1092–1099). The Guidelines set forth the utility criteria: specific, substantial and credible. See also main opposition arguments and considerate answers to them.

An amendment to the US Patent and Trademark law (Bayh Dole Act) in 1980 allowed patentability and also inventions born in the context of research funded by federal money (academia). Universities established Technology Transfer Centres to manage the patents and out licensing. However, the increase of patents has had a negative impact to the traditional open science culture in the United States.

National Research Council of the National Academy of Sciences has studied the subject of granting and licensing of intellectual property rights on discoveries relating to

genetics and proteomics and the effects of these practices on research and innovation. (Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health. National Academy of Sciences 2006 Forthcoming, see www.nap.edu/catalog/11487.html.) It provides several recommendations to create an environment in which it is possible to foster scientific advances and enhance human health, and which avoids conflict between open dissemination and access to scientific discoveries and the inventors' rights.

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