
2

The current landscape

2.1 Intellectual property systems

A patent is valid only within a particular jurisdiction. For instance, a patent granted by the USPTO provides rights over a given invention within the United States of America. Third parties are excluded from making, using or selling the invention within the borders of the United States and its territories, including importing the invention into the country.

An inventor can seek patent protection in multiple jurisdictions through a single application. The African Regional Industrial Property Office (ARIPO), an organization of eastern and southern African countries, is an example; a single application can provide patent protection across all 15 countries that belong to ARIPO, although national offices still need to register patents in accordance with national law. By contrast, in the African Intellectual Property Organization (OAPI), an organization of West African countries, there is a truly regional patent. In Europe, an applicant can apply to one or more national patent offices, or can apply for a patent from the EPO, which is recognized in countries party to the European Patent Convention. A national patent is valid in that country; an EPO patent can be recognized in multiple countries designated by the inventor. Infringement actions, however, must be litigated in national courts. The EPO is the administrative body of the European Patent Convention, which covers all European Union

(EU) Member States as well as some non-EU countries. Since 1975, there has been discussion about creating a single patent (the Community Patent) for the whole of the EU.¹¹ The Patent Cooperation Treaty (PCT) permits inventors to apply through the World Intellectual Property Organization (WIPO) for patent protection in 123 countries, but patents are only actually granted at the national level.

Globally, the EPO, USPTO, and Japanese Patent Office (JPO) are the most influential actors in international patent policy, and regularly meet in trilateral discussions.¹² WIPO plays a major role in the administration of international agreements, and the WTO has become a key institution as a result of the 1995 Agreement on the Trade-Related Aspects of Intellectual Property Rights, which emerged from the Uruguay Round of trade negotiations of 1994 that also established the World Trade Organization.

Despite the creation of various international frameworks, and the streamlining of patent application processing across some jurisdictions, patent legislation is nevertheless designed and applied principally at the national level. It is therefore important that each country weigh domestic factors when constructing its patent regime. However, national patent regulation is heavily constrained by the requirements of TRIPS.

Under TRIPS, WTO Members are obliged to provide minimum standards of protection for a wide range of intellectual property rights, incorporating many of the provisions from existing agreements administered by WIPO, like the Paris Convention of 1883 and the Berne Convention of 1886. With regard to pharmaceutical patents specifically, TRIPS requires that all nations (except least developed countries) adopt the practice of accepting pharmaceutical product claims as patentable by 2005 at the latest. The WTO Doha Declaration of 2001 reaffirmed that the TRIPS Agreement “can and should be interpreted and implemented in a manner supportive of WTO Members’ rights to protect public health and, in particular, to promote access to medicines for all” (WTO, 2001; WT/MIN(01)/DEC/2).

However, the implementation of the Doha Declaration was contentious, in particular resolving the issue identified in paragraph 6 of the Declaration. Article 31(f) of TRIPS states that products made under compulsory licensing must be “predominantly for the supply of the domestic market”. A compulsory license is a government-authorized use of a patented invention without the patent holder’s consent, and is permissible under Article 31 of TRIPS, provided that certain conditions are met. In paragraph 6 of Doha, the WTO recognizes that WTO Members with insufficient or no manufacturing capacity in the pharmaceutical sector could have difficulty making effective use of the compulsory licence safeguard, originally expressed in TRIPS and clarified in the Doha Declaration (WTO, 2001; WT/MIN(01)/DEC/2).

On 30 August 2003, after protracted negotiations, member countries finally agreed “to allow any member country to export pharmaceutical products made under compulsory licences” (WTO, 2003; WTO Press/350/Rev.1). Eligible developing countries now have the option of importing generic drugs produced under compulsory licences overseas, which they would not be in a position to produce domestically, in order to address local public health challenges.¹⁶ All compulsory licences

would be required to comply with the agreed terms and it was understood among the members that the decision would be “used in good faith in order to deal with public health problems and not for industrial or commercial policy objectives” (WTO, 2003; WTO Press/350/Rev.1).

The present reality is that many developing countries lack not only sufficient scientific capacity to manufacture patentable products but also the necessary infrastructure and capacity to construct and implement finely balanced patent systems (Carroll, 1995). There is concern that they may be obliged to institute “TRIPS plus” legislation nationally (e.g. as a result of bilateral trade agreements), which does not take advantage of the flexibility and public health safeguards within TRIPS (Musungu and Dutfield, 2003).¹⁴

2.2 TRIPS and DNA patents

In relation to DNA patents specifically, there is contention as to whether TRIPS requires countries to grant patents on DNA sequences. While the TRIPS Agreement does not explicitly obligate its members to declare DNA sequences to be patentable inventions, Article 27(3) does not list DNA or genes among the acceptable exceptions from patentability. According to Article 27, “patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application”. However, it stipulates that:

3. Members may also exclude from patentability:
 - (a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals;

Box 7 Research exemptions

TRIPS, in section 30, states that members can provide limited exceptions to the exclusive rights conferred by a patent. Section 8 of TRIPS permits members to adopt measures necessary to protect public health and nutrition and to promote the public interest in sectors of vital importance to their socioeconomic and technological development.

Some countries have adopted research exceptions (also called research exemptions) in their patent legislation, which grant a limited right to researchers to experiment on a patented invention. They may also enable researchers to undertake studies to gain a fuller understanding of the invention itself without having to pay royalties to the patentee. But there is sometimes uncertainty about the scope of a project permitted by a research exception clause, especially in the case of research dealing with genetic material. In the United States of America, a recent case (*Madey v. Duke*, 2002) has severely limited the research exemption in the country's universities.

Some developing countries have also integrated a research exception clause into their patent legislation. For example, the Brazilian Patent Law states that "experimental working for scientific or technological research purposes" qualifies as a research exception (Brazil: Patent Law 9.279 of 1997).

In India, section 47(3) of the Patent Act of 1970 excludes from the exclusive patent right "any machine or other article in respect of which the patent is granted and any process in respect of which the patent is granted may be made or used by any person, for the purpose merely of experiment or research including the imparting of instructions to pupils". Amendments to the India Law in 1999 and 2002 have retained section 47(3) as crafted in 1970.

The Patent Law of the People's Republic of China states in section 62 that using the patent concerned solely for the purposes of scientific research and experimentation is not considered to be an infringement of the patent right.

A number of recent reports have expressed the need for greater clarity regarding what is covered by research exemptions, particularly in relation to clinical and preclinical research (OECD, 2004; Nuffield, 2002). This environment creates significant uncertainty for researchers who may become hesitant to undertake projects where they need to rely on ill-defined exemptions. Researchers may rightly fear having to face patent infringement suits, which could be very expensive.

(b) plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes. However, Members shall provide for the protection of plant varieties either by patents or by an effective *sui generis* system or by any combination thereof. The provisions of this sub-paragraph shall be reviewed four years after the date of entry into force of the WTO Agreement.

What is relevant for our purposes is that nowhere in paragraph 27.3(b) is reference made to genes or DNA. This means that countries are free to judge for themselves whether the excludability of DNA is inferred, and how strictly to apply the three criteria of patentability. Brazil, for example, has chosen not to permit the patenting of "the genome or germ plasm of any natural living being, when found in nature or isolated therefrom, and natural biological processes" (Section 1, Article 10 IX of Industrial Property Law No.9279/96). On the other hand, Brazil will allow use of patents based on gene sequences.

By contrast, DNA patents have been permitted in Europe and the United States of America for many years. The European Parliament and Council *Directive on the Legal Protection of Biotechnological Inventions 1998* or the EU Biotechnology Directive (*EC, 1998; 98/44/EC*), adopted after a 10-year debate in the Council and European Parliament, requires that biotechnological inventions that meet the criteria of novelty, utility and non-obviousness be deemed patentable, with few exceptions. However, most EU Member States are still to implement the Directive, because of widespread concern about the implications of patenting biological substances. In Article 5, the Directive states:

1. The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.
2. An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.
3. The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application.

While some countries' reluctance to implement the Directive may, in principle, speak of hesitance or opposition, it arguably has little consequence in practice; the majority of patent applications go through the EPO, which has incorporated the Directive, and these patents may be validated by

national patent offices, even in those countries that have not yet implemented the Directive.

This debate reflects a fundamental controversy about whether DNA ought to be treated specially, or the same as any other molecule. Many naturally occurring chemicals, like erythropoietin, have been patented by companies that have succeeded in isolating them in the laboratory.¹⁵ In section 3.1 we will consider some of the concerns about the eligibility of DNA as patentable subject matter. As we saw above with Brazil, developing countries have responded differently to the issue of how to treat DNA, in the context of patent law. We will explore some of these differences in section 2.4.

2.3 The genomics industry and patenting

Genomic industries are those that employ genomics approaches—namely, sequencing, high-throughput screening, DNA microarrays, other DNA methods, bioinformatics and data mining—as an important part of their business model. Firms in this category may be engaged in a range of activities, from drug discovery and development, through the creation of diagnostics to producing research tools and methods. In this section, we will identify the major actors in this field, both public and private, and consider how DNA patents are implicated in their activities.

2.3.1 Who is doing the work and where

When the Human Genome Project got under way in the late 1980s, investment in genomics from the private sector was very low. However, by 1993, public and private funding of genomics in the United States had reached nearly equivalent levels. According to an international survey conducted in 2000, the private sector is now the predominant source of funding for genomics, and the United States accounts for the lion's share of this investment. Indeed, the six biggest players in

genomics are United States firms (Cook-Deegan, Chan and Johnson, 2000).

Like biotechnology, genomics is an approach, rather than a specific field. And like biotechnology, genomics has infiltrated many fields that use its large-scale, highly automated methods for the study of DNA. Firms engaged in genomics activities include service firms that sequence or analyse DNA for research laboratories; firms that carry out genetic testing or forensics; firms that make instruments; and firms that develop analytical software used to analyse entire genomes, mine DNA databases, or interpret data. The top four genomics firms in the United States, which include Celera Genomics, have different business models, and are therefore engaged in varying combinations of the above activities (Cook-Deegan, Chan and Johnson, 2000). Genomics firms like Myriad Genetics and Quest Diagnostics, for instance, are involved in developing genetic tests. In general, “diagnostics firms” invest considerable capital into the development of highly systematized, automated methods for the accurate diagnosis of particular diseases.¹⁶

In contrast to companies that are centred on the sequencing and analysis of genomic DNA, some companies have complex business strategies that require the large-scale sequencing of genes, as well as the production of proteins whose medical value must be assessed in order to develop new genomic pharmaceutical products. Though their work is “gene-based”, as it were, these companies are in the business of creating not only diagnostics, but also therapeutics. They may face, therefore, high front-end costs of research and development similar to those confronted by traditional pharmaceutical firms.

In the pharmaceutical sector, innovation costs are generally very high (DiMasi, Harsen and Gatowski, 2003), and there may be on average 8 to 12 years between patenting a new product and bringing it to market. Average costs are high because only a small proportion of investigated products gives rise to marketed drugs. In this setting, patents are considered a critical factor in providing incentives for research and development

(R&D), as well as protecting competitive advantage. They are also prized by start-ups and university spin-off companies in the biomedical field, whose main asset for attracting venture capital is protected intellectual property (OECD, 2004).

By contrast, in-house genetic tests can often be developed with relatively little expense, using existing and accessible methods from biotechnology, once the relationship between the gene and the disease has been established. These laboratories are often proficient at producing low-cost diagnostics based on published information, and do not require the high front-end investment in product development of commercial firms. Consequently, examples exist of straightforward, reliable methods for testing for genetic disorders like sickle cell disease and cystic fibrosis. But while these tests fill an immediate need, by providing simple-to-use and inexpensive diagnostic tests for locally relevant conditions, they vary widely in terms of their protocols and safety testing, because in-house tests are also generally subject to less rigorous standards (Cox et al., 2003).

The link between diagnostics and therapeutics is increasingly strong, which could mean that the economics of diagnostics and therapeutics will converge in the coming years. We discussed in section 1.3 the advent of genomic medicine. This employs genomic information to provide more personalized care for patients, which is based on evidence that some patients respond more poorly to certain treatments. In December 2003, the worldwide vice-president of genetics at GlaxoSmithKline stated: “The vast majority of drugs—more than 90 per cent—only work in 30 or 50 per cent of the people” (Connor, 2003). Some companies are already exploiting such pharmacogenetic indicators to develop genetic tests to determine if patients will benefit from specific drugs, or will have unusual toxic reactions to them (Service, 2003). For now, this work is directed towards only a few conditions, including some forms of breast and colon cancer, and some drug classes for pain control. As understanding of the genetic basis for drug responses grows, genetic tests may precede use of many therapies to increase the likelihood of a positive outcome or to reduce side

effects. This is particularly important for expensive treatments, and when several possible therapies are available, with varying costs and side-effects. The 2003 Nuffield Council on Bioethics report on pharmacogenomics claims: “It is not clear that the private sector will be motivated to pursue pharmacogenetics research in relation to medicines not covered by patent protection”.

The report further recommends that:

Efforts should be made to encourage pharmacogenetics research on existing medicines, where there is reason to believe that such research could significantly improve efficacy or safety. Funding within the public sector and public-private partnerships should be encouraged.

2.3.2 Trends in patenting

Entities from industrialized countries currently hold 97% of all patents worldwide. More than 80% of the patents granted in developing countries belong to residents of industrialized countries, usually multinational corporations from the most advanced economies. 70% of global royalty and licensing fee payments are made between parents and affiliates of multinational corporations (UNDP, 1999). Developing countries do not represent a significant percentage of patent applicants. It is estimated that only 0.1% of the total number of patents issued by the USPTO, including all varieties of patents, were filed by sub-Saharan African applicants (Ogbu, 2002).

The rise in patents in biotechnology has been particularly dramatic, climbing by 15% per annum from 1990 to 2000 at the UPTO and 10.5% per annum at the EPO, compared with a 5% per annum increase in overall patents (OECD, 2004), though there has been a notable drop in the past three years in the number of DNA patents granted. As of 2003, more than 5000 applications for patents on human genes had been filed with the USPTO and from

those applications more than 1500 patents were granted (Kluge, 2003). Inventors from the United States have filed more international patents on DNA sequences than inventors anywhere else in the world, and more than the combined total of inventors in the European Union. Japanese and British inventors are the next most prolific patentees in this field (Rausch, 2002).

The public sector has played an important role in the growth of patents for biotechnological inventions. For example, public institutions in Europe and the United States own 30% of all the patents for DNA sequences filed between 1996 and 1999. And start-up companies have a higher share of biotechnology patents than do large, established pharmaceutical companies (OECD, 2004). In the United States, the Bayh-Dole Act of 1980 introduced incentives to universities receiving federal funding to patent the products of their research, in order to encourage technology transfer, and the commercialization of inventions into useful products. The result is that some universities today own more DNA patents than do large private firms (Cook-Deegan, Chan and Johnson, 2000). There is ambiguity for those centres that provide diagnostic testing services. To improve existing techniques and test efficacy, research requires that tests be used on patients, which amounts to providing clinical services. While a number of countries provide a research exemption (see section 2.3.3) that permits the use of patented subject matter for strictly research purposes, it is not clear to what extent this exemption applies to institutions whose research involves the use of patient samples and thus overlaps with clinical practice (Walsh, Arora and Cohen, 2003; Cornish, Llewelyn and Adcock, 2003).

One of the difficulties in cases where university laboratories are among the chief providers is that universities are increasingly viewed as pursuing commercial ends, being actively engaged in profit-making activities and in widespread patenting and licensing (Howard, 2004). Consequently, some have judged it a double standard that universities would be spared having to pay licensing fees for

services provided, when they themselves are likely holders of rent-earning patents. Although this is not the case with all universities, their supposed immunity because of their status as academic centres may be in danger of disintegrating in the face of increasingly profit-making agendas.

Traditionally, governments have had the role of filling the gaps; of addressing market failure by allocating funds to areas of research that draw little funding from private sources. However, if those institutions receiving public funding are increasingly tied to the private sector and are licensing their inventions exclusively to companies, public money may be generating products that are not readily accessible to the public (e.g. because of high prices). Products may not be developed for needy populations as these generally do not constitute lucrative markets. Given that the effectiveness of the patent system relies on market mechanisms, this situation, at least in principle, presents a tension between the aims of government-funded research and the incentives that underpin the patent system; and the further challenge is that publicly funded research does not always find its way into the public domain. However, licensing practices and policies may in future play an important role in leaving open avenues of research relevant to developing countries. For example, research-use exemptions or humanitarian-use exemptions, which protect from litigation research in areas of primarily humanitarian rather than commercial interest (such as adapted tools for use in low-resource settings) are being explored by several groups. The idea behind such work is to develop ways of changing norms around licensing, so that innovation in areas outside of market interest is not impeded.

Developing countries stand to gain from taking advantage of the flexibility within TRIPS that allows members to protect researchers from infringing patents used in research. Such clauses can encourage research activity, and foster the development of scientific capacity. However, they should be careful to avoid ambiguity in defining the scope of the research exemption, because a lack of clarity may chill research. In the face of uncertainty, researchers are reluctant to risk patent

infringement and possible litigation. It is therefore particularly important to clarify how the research exemption applies to preclinical and clinical research that has the dual aim of advancing knowledge and producing or providing goods and services.

2.3.3 Opportunities and challenges for developing countries

In most cases, companies do not bother to take out patents on DNA sequences in developing countries, because the market in those countries is not lucrative enough to warrant protecting. What is at stake is the development of cheap technologies suitable for use in the developing world, given the current make-up and emphasis of the genomics industry. Endogenous research within most developing countries may not be hindered by patents; however, research may be hindered in those countries with adequate technological capacity and research capital to generate the products of relevance to their poorer neighbours. These countries include the United States, where, as we have seen, the bulk of genomics-related research is taking place. They could also include Brazil and India, developing countries with well-advanced science and health technology sectors, which are well placed to generate appropriate health-related products to address local and more global needs.

An interesting place where advances are being made in genomics is in bioterror-related research. As genomics provides tools for studying pathogens and developing ways of diagnosing them quickly and simply, it can do the same for “bioterror” agents and therefore holds great interest for some defence programmes. Platform technologies used for bioterror research can be relatively easily adapted to create applications relevant to developing countries. Some academic researchers interested in creating such tools have capitalized on grants for biodefence research to create technologies for the diagnosis and monitoring of infectious diseases, like HIV/AIDS.

Much of the promise in genomics and biotechnology for developing countries depends

on using platform tools and technologies, modified for use in poorer settings. The work of Dr Eva Harris is a well known example of technology transfer of biotechnology tools to low-resource settings, primarily in Latin America. She is free to teach local laboratory technicians and health care workers how to create low-cost alternatives to technologies used in her own laboratory at the University of California at Berkeley, because patents on the technologies do not tend to exist in those countries. Whether she would have the same liberty to work in poor countries with more well-developed biotechnology sectors where patents on genetics tools may be more likely, is less clear. Dr Harris must carry out most of her teaching on-site because she risks patent infringement doing the same work at home. Likewise, work in universities using platform technologies can be modified for use in developing countries. A research technology, developed through a collaboration between the Sustainable Sciences Institute (SSI) and the University of California at Berkeley's Department of Electrical Engineering and its School of Public Health, has generated a low-cost point-of-care tool for diagnosing dengue fever. According to its creators:

The ImmunoSensor is a platform technology, thus it can be adapted for virtually any disease that is currently diagnosed by an immunological assay. The prototype application of the ImmunoSensor is diagnosis of dengue, the most prevalent mosquito-borne viral illness, with 100 million cases of dengue fever annually worldwide. SSI is coordinating field trials for dengue diagnosis using the ImmunoSensor in Nicaragua, Ecuador and Sri Lanka. In addition, efforts are being spearheaded to adapt this technology for HIV diagnosis.¹⁷

SSI is presently negotiating rights to ImmunoSensor technology from the University for use in developing countries, and will develop a

business strategy so that disease-endemic regions can use and market the product to serve their own needs. The underlying IP of platform technologies could be safeguarded for applications such as this.

As for pharmacogenetic approaches for personalized treatment, it will likely be an important part of the way medicine is practised in the future. There are a few examples today of its successful use, though there remain big questions about when, and if, it will come into widespread use. What is important to remark is that pharmacogenetics presents a further example indicating that as medicine continues to evolve, it is likely that the importance of genetic tests will grow, and their usefulness expand considerably beyond tests for genetic disease. Competency in the development and delivery of genetic tests could therefore provide a foundation for continuing benefit from medical advances based on genomics. However, ensuring that personalized medicine will be an affordable option in general, and for developing countries in particular, presents a major future challenge. Moreover, the application of pharmacogenomics in developing countries is likely to be quite different from in Europe and Japan, for instance. The disease burden in poorer countries is not identical—for example, infectious disease is still a major problem—and health systems require adapted methods. The direction of genomic research today is the direction that current incentives encourage—and is one that does not show any signs today of targeting the needs of those outside of wealthy markets. We will consider in later sections in more detail the role of patents in guiding the shape of today's research landscape.

2.3.4 Availability of genomic data

The availability of fundamental genetic data is not solely dependent on public funding. For example, the SNP Consortium was a collaborative venture among 10 private sector companies and the Wellcome Trust. It was “founded on the premise that genetic information related to SNPs is accelerated when research findings are freely

available to all researchers and companies” (<http://snp.cshl.org>). The Consortium was a not-for-profit group working to compile a database of mapped SNP, whose contents are freely available through free public databases. SNPs are common DNA sequence variations among individuals, which scientists hope will improve their ability to understand and treat human disease. According to the Ontario Ministry of Health and Long-Term Care (2002), this project “treats SNP information (non-patented) as primarily an informational input freely available, and yet, still providing a vital contribution to downstream product development”.

One commentator has argued that large companies, in fact, see it as being in their interest to free up raw data:

Although it may seem extraordinary for firms that usually sing the praises of the patent system to collaborate in a concerted effort to put new discoveries in the public domain, it makes perfect sense from the perspective of the pharmaceutical industry. The patents that matter to pharmaceutical firms are the drug patents that secure the revenues that fill the pharmaceutical feeding trough. Patents on the many prior discoveries that facilitate drug development look like siphons, diverting those revenues to the troughs of other firms (Eisenberg, 2001).

This suggests that big companies may not all be opposed to liberating research tools from patent protection.

Intellectual property rights covering databases represent the second major way in which proprietary rights may be exercised over DNA sequences. In some countries, databases are protected by copyright or *sui generis* database rights, though in the United States, unlike in the EU and elsewhere, they are protected mainly by contract law — agreements signed by users to gain access to databases.

As previously noted in section 1.3, the Human Genome Project exemplifies the fact that by no means all genetic inventions are protected by patent rights. In fact, the HGP has been used as an example of precisely the kind of scientific effort that did not require the incentives of patents to promote innovation, and indeed actively discouraged patenting on the pathway to producing the reference sequence. The project, which was entirely publicly funded, was characterized by both openness with respect to the sharing of results, and competition among laboratories.

The HapMap project, which aims to “determine the common patterns of DNA sequence variation in the human genome and to make this information freely available to the public” (International HapMap Consortium, 2003), has adopted a different approach, applying the software model of open-source access, which permits others to use its products on condition that they too agree to keep them in the public domain (Cukier, 2003). While the HapMap project allows process patents, it does not allow product patents on DNA sequences. It is less open than the HGP, but aims to protect the products generated from its work from being used by private entities that could make proprietary claims, limiting access to communal resources.

Despite the SNP Consortium and other similar examples, there were in the late 1990s a number of firms that charged for access to databases of genomic sequences. But lately the relative value of private versus public databases has been called into question by the announcement that Incyte Corp., the largest genomics firm in the United States, is closing its headquarters and paring more than half of its workforce. According to a brief in *Science*:

The gene discovery firm [Incyte] pioneered the notion of turning profits by selling genetic data to drug discovery firms and academics. The strategy seemed promising for a while, and the company’s stock bolted to the dizzying high of \$144 a share during the technol-

ogy bubble days of 2000. But the company faced the stiffest competition possible: free genomic data supplied by public gene-sequencing efforts financed by governments around the globe.... Like other one-time genomics companies such as Celera and Myriad Genetics, Incyte has refashioned itself as a drug discovery firm (Service, 2004).

This suggests not only that efforts to generate genomic data have been highly productive to date, but that the resulting publicly available data is generating arguably more useful follow-on research by companies that have turned to drug discovery, unable to sustain a business model based on privately-owned data. While the race to sequence the human genome was a fruitful and largely efficient one, translating this wealth of knowledge into applications has been much slower—though, arguably, it has been facilitated by largely free access to sequence data. Whether the lag in generating useful products is due to the unavoidable complexity of the work involved, reflects fundamental flaws in the research and development chain, or a combination of both, has yet to be elucidated.

What is clear is that, thanks to the abundant success of the HGP and other initiatives, there is a growing repository of publicly available genomic data. Researchers in developing countries can benefit from access to these resources. Existing strategies to develop indigenous capacity in bioinformatics and data mining in low-resource settings, including through international partnerships, should be identified and assessed, and initiatives considered to encourage these efforts.

The Human Genome Project was characterized by competition, openness in the sharing of results, and efficiency. The international HapMap project, for its part, has adopted an open source approach for providing access to genomic data, while preventing third parties from making proprietary claims that could restrict access. This approach, while promising, has yet to prove itself; moreover,

while the HGP and HapMap models are arguably effective ways for encouraging and sharing the fruits of basic research, it remains very unclear whether they provide the right kind of incentives for the work required to translate this research into applications. Large companies have shown their willingness, in some instances, to engage in more open science when it involves the generation of raw data.

The open source model for genomics has been advanced by several scholars. We will consider it, and various other models, in section 3.2.2 below.

2.4 What some developing countries are doing

There is great diversity among developing countries, including wide diversity in scientific capacity and infrastructure to support health research and health delivery, as well as varying patent systems. Although they are different in a number of respects, Brazil, China and India are all examples of developing countries with comparatively well developed gene-based industries. In this section, we will consider the capacity of each of these countries to harness gene-based approaches to address the needs of their populations. We will also look at the patent systems that have developed over time and helped to shape their present circumstances.

2.4.1 Brazil

Genomics in Brazil

The State of São Paulo Science Foundation or FAPESP, was founded in 1962 in São Paulo, Brazil's richest and most populous state (37 million people). In 1997, FAPESP, established the Organization for Nucleotide Sequencing and Analysis (ONSA), a virtual community including 35 laboratories across the state (*Economist*, 2000), which was charged with boosting Brazilian competence in genomics. ONSA's first project was to sequence

X. fastidiosa, a bacterium that causes citrus variegated chlorosis (CVC), which results in fruit that are small, hard and of no commercial value. CVC was first recorded in Brazil in 1987; it affects all varieties of sweet orange (Simpson, 2000) and has a significant economic impact, costing Brazilian growers an estimated US\$ 100 million per year (*Economist*, 2000).

The successful sequencing of *X. fastidiosa* provided FAPESP with both a team of skilled sequencers who were then able to move on to sequencing genes relating to human diseases, and international recognition that has resulted in external funding for human-related sequencing projects. The *X. fastidiosa* genome was the first complete sequence to come from outside the United States, the United Kingdom or Japan and the first ever sequencing of the complete genome of plant-disease-causing organism (Yoon, 2000). FAPESP's approach was novel because it created a virtual research community rather than investing in building a physical genomics centre (Trafford, 2001). FAPESP's statute prohibits it from assembling its own corps of scientists. The institute must, therefore, invest widely in existing centres within the state rather than confining resources to a small subset of the research population. This results in the sharing of knowledge among a large number of researchers and a sustainable investment in the industry.

The virtual network strategy allowed ONSA to maximize the value of the funding provided by FAPESP, to overcome geographical isolation and to nurture a critical mass of trained geneticists. The success of the *X. fastidiosa* project catapulted Brazil into the international spotlight. As a result ONSA has developed international partnerships to fund further sequencing projects that are expected to make a significant contribution towards better understanding of leading causes of ill health globally. For example, ONSA is sequencing human cancer-related genes in collaboration with the Ludwig Institute in Switzerland (Rother, 2001), which is paying half of the US\$ 10 million cost of the project (*Economist*, 2000).

In 2000 the Federal Government of Brazil decided to expand São Paulo's genome project to the national level; it launched the Brazilian Genome Project, which comprises a network of 25 sequencing laboratories. The growth and strength of genomics industry in Brazil indicate the results of these initiatives. For example, the number of scientific publications from Brazilian researchers increased 300% between 1987 and 2002, now accounting for about 1.2% of global scientific papers. Brazil is now an undisputed leader in plant genomics (WHO, 2002).

Brazil's patent law

In 1809 Brazil became the fourth country in the world to enact a patent law. Brazil became a founding member of the Paris Convention in 1882 (Barbosa, 2004). On 14 May 1996, Brazil introduced Law No. 9.279 to Regulate Rights and Obligations Relating to Industrial Property (Brazil Law, 1996), which was intended to fulfil Brazil's obligations under TRIPS to enact minimum patent standards (Barbosa, 2004).¹⁸

Brazil signed the Convention on Biological Diversity (CBD) in 1992 and ratified it in 1994. Brazil has been a vocal and active supporter of benefit sharing in relation to the commercialization of research based on natural products and of introducing an internationally recognized certificate of origin for genetic samples (GRAIN, 2002). After extensive negotiations at the Seventh Meeting of the Conference of Parties to the Convention on Biological Diversity in Kuala Lumpur in February 2004, country representatives agreed to include the certificate of origin as a topic to be addressed in the guidelines to be prepared by the next conference in Brazil in 2006 (Dalton, 2004). As we will see in section 3.1.2, CBD specifically excludes human genetic resources.

In 2001, the United States filed a complaint with the WTO arguing that Article 68 of Brazil's patent law No. 9.279 was in breach of Articles 27 and 28 of TRIPS. Article 68 allows Brazil to issue a compulsory licence to a local producer if, after

three years, the patent holder has not begun manufacturing the product in Brazil. This measure is designed to encourage technology transfer and support a strong domestic generics industry, in addition to strengthening the Brazilian Government's bargaining position in relation to the cost of drugs (Oxfam, 2001) and, ultimately, helping the Brazilian Government to ensure affordable access to vital medicines (Cooper, 2001).¹⁹ Though the case involving drugs has become the prototype for considering compulsory licences, particularly in the context of developing countries, it is important to recognize that compulsory licences are not limited to use against drug companies. For instance, in France, opponents to restrictive licensing of genetic tests threatened to opt for *ex officio* licences, permitted by French law on grounds that practices are contrary to public health (Lecrubier, 2002).

Gene patenting

According to a report prepared by the Brazilian Group of the International Association for the Protection of Intellectual Property (AIPPI), there is ambiguity as to whether the Brazilian patent law No. 9.279 excludes genes from patentability. Both Article 18, item III, and Article 10, item IX, suggest that genes should not be considered patentable material. On the other hand, the law does allow for the patenting of chemical products, provided they fulfil the criteria of novelty, inventive activity and industrial application. If Brazil were to conclude that DNA is not merely a large polymer, it could permit chemical product patents while blocking patents on genes.²⁰ At the time of writing of the Brazilian Group's report there was no case law to resolve this issue of interpretation.²¹ However, a number of commentators have concluded that DNA is not patentable under current Brazilian law—except for certain specific uses.²²

2.4.2 China

Genomics in China

China has adopted a policy of actively supporting and encouraging biotechnology and genomics-related industries. In 1998 the Ministry of Science and Technology established both the Chinese National Human Genome Centres (CHGC) in Shanghai and Beijing to specialize in genome sequencing and analysis (WHO, 2002). In 1999, the Chinese Academy of Sciences established the Beijing Genomics Institute (BGI). China was then in a position to join the International Human Genome Sequencing Consortium in 1999. China not only played a significant role in the sequencing itself, characterizing 1% of the human genome, but was able to develop advanced bioinformatics and supercomputing facilities to support further genome-sequencing research. This research has included sequencing the silkworm genome, establishing the Super Hybrid Rice Genome Project and collaboration with Danish scientists to sequence the pig genome (Porcine Genome Sequencing Project).²³

BGI's latest achievement was announced on 1 March 2004, when BGI reported the construction of a chicken genome variation map, based on DNA from three strains of chicken and identifying two million SNPs. This work is part of a larger project to sequence the chicken genome, conducted by an international team and lead by BGI.

China supports collaboration with foreign researchers, but recognizes the need to protect Chinese genetic resources from exploitation and biopiracy (WHO, 2002). In 1998 the Ministry of Health and the Ministry of Science and Technology jointly established the Chinese Human Genetic

Resources Management Office. It is responsible for managing all matters dealing with Chinese human genetic resources, including human gene groups, blood, genes, organs, cells and other DNA materials of human beings (Feng, 2003).

China is keen to ensure that some of the benefits of international genetic research, based on Chinese genetic samples, flow back to the Chinese community. Yu Xiucheng, director of the Division of Health Technology Management of the Department of Sciences, Technology and Education of the Ministry of Health has stated that all cooperative international projects based in China and working with Chinese human genetic resources should follow the principles of equality, mutual benefit and joint participation; and that the achievements and patents must be owned and shared by both the foreign and domestic researchers (Feng, 2003).

China's patent law

China first introduced a patent law in 1985, which was subsequently revised in 1992. Further amendments to bring the patent law in line with international standards and TRIPS requirements were passed at the 17th Session of the Standing Committee of the Ninth National People's Congress, and took effect on 1 July 2003.²⁴ For example, the amended law will, in accordance with TRIPS, allow patent holders who believe their rights are being infringed to ask the courts to intervene.²⁵

During the same period, as China prepared to join the WTO, the overall number of patent applications increased. By the end of July 2001, the State

Intellectual Property Office of China had accepted 99 550 patent applications from China and abroad, a 24% increase from 2000.²⁶

Gene patents

Chang Mao, an officer from the State Intellectual Property Office, has stated that China does not allow companies or research institutes to patent life forms; however patenting genes is permissible (Wang, 2001).

In 2001, Shanghai Joint Gene Technology Co. Ltd, the largest gene technology company in China, applied for more than 3700 gene patents, including patents for genes dealing with cancer, obesity, high blood pressure and senile dementia, which are expected to be of high value for clinical diagnosis and the development of new medicines. "Owning intellectual property is one of our company's fundamental goals. If we had not owned intellectual property, we would not have our own gene industry after WTO accession", said Qin Yilong, the company's vice-president in 2001.²⁷

The concept of *international patent families*²⁸ provides a basis for comparing the research and technological activity of different countries, in terms of resulting products intended for international use. A *patent family* consists of all the patent documents associated with a single invention that are published in one country. From 1980 to 1999, China, which had filed a total of 145 patent families in human DNA sequences, had only filed 17 international patent families.²⁹ The United States, by comparison, had 5610 international patent families (accounting for 72% of the total world figure of 7810).³⁰ Brazil had only 1 international patent family.

2.4.3 India

Genomics in India

The growth in the biotechnology industry in India is built upon its existing internationally recognized information-technology industry, a large pool of trained scientists and a dynamic generic pharmaceutical industry (BioSpectrum, 2003). In the international market, India's highly qualified, English speaking but comparatively low-cost workforce offers a significant competitive advantage (Thorold, 2001). The Indian Government has invested substantially in building the industry. The Department of Biotechnology (the Department) was established by the Indian Government in 1986 and receives an annual budget of approximately US\$ 30 million (WHO, 2002).

The Department has established a programme in Human Genetics and Genomic Analysis, which includes projects in genetics diagnosis and counselling, functional genomics, research into human genome diversity, and biocomputing. There are 16 Genetic Diagnosis and Counselling Units throughout India, which have provided genetic testing and counselling services for over 18 000 patients and families affected by genetic disorders such as thalassaemia, sickle cell disease, Duchenne muscular dystrophy (DMD), haemophilia, and cystic fibrosis.³¹

In recognition of the connection between information technology and biotechnology, the Department initiated a bioinformatics programme in 1986. This programme gave rise to the Biotechnology Information System Network, which operates throughout India, and has resulted in the development of state of the art computational and communication resources that are used to support sophisticated bioinformatics research. India now operates as a "major regional nodal point for genomic-related databanks and networks" (WHO, 2002). In addition, the Indian Government recently approved a programme in molecular genetics and genomics with an annual budget of US\$ 4 million, to be administered through the Indian Council of Medical Research (WHO, 2002). Furthermore, the Indian Ministry for Science and

Technology has invested in a number of centres of excellence in the field with world-class infrastructure and staff, such as the Plant Genomics Centre, New Delhi, and the Centre for Human Genetics, Bangalore.³²

States like Andhra Pradesh, Karnataka, Maharashtra, Kerala, Tamil Nadu and Himachal Pradesh are developing biotech parks and biotech-friendly policies, which include a number of concessions for foreign industry partners.³³ Two highly successful biotech firms are Shanta Biotech and Bharat Biotech. Shanta Biotech produces India's first genetically engineered vaccine called Shanvac (BioSpectrum, 2003), which vaccinates against hepatitis B. Shanvac retails for US\$ 4 which is less than half the price of similar vaccine sold by multinational companies.

Patent law in India

India's original Patent Act was passed into law in 1970 (Singh and Agarwal, 2003). TRIPS entered into force in 1995. The Patent (First Amendment) Act 1999 provides transitional patent protection, as a step towards becoming fully TRIPS compliant, by implementing Exclusive Marketing Rights (EMRs). EMRs are particularly important in relation to drugs and food, because India will not allow product patents until 2005. EMRs provide exclusive rights to *sell* one's patented products, whereas full product patents grant exclusive rights to *both* manufacture and sell the products. The EMRs protection period is five years.³⁴ Under the 1999 Amendment, it is now possible to make an application for product patents, including substances intended for use or capable of being used as a medicine or drug, but excluding the intermediate for the preparation of drug. However, because India has until 2005 before its patent legislation must be fully TRIPS compliant, product claims for medicines or drugs will not be processed until the end of 2004.³⁵

The Patent (Second Amendment) Act 2002 and the Patent Rules 2003, which came into force on 20 May 2003, include provisions for extending the patent term to 20 years and emergency provisions

to protect public health. These amendments will bring the Indian patent regime further in line with TRIPS. Indian law used to provide a standard period of 14 years protection (from the date of sealing) and 5 years protection (again from the date of sealing) for food and medicinal products. This has been increased to a protection period of 20 years.

In order to protect indigenous knowledge, an exemption for products based on Indian systems of medicine has been granted. Section 3 of the Patents Act explains that an invention that is in fact traditional knowledge is not patentable. Nor does the Indian patent system appear to allow patents on genes or cells.³⁶

2.5 Some early lessons for developing countries

Each of three countries described above has achieved a level of competence in gene-based research and its applications. Though there are diverse and complex economic, historical and cultural factors at work, it may be useful to highlight those features that are common to all three countries:

- political commitment to building strong national biotech industries, supported by financial resources;

- a clearly defined project, highly relevant to local needs around which to mobilize efforts;
- an emphasis on building sustainable networks across the country;³⁷
- capitalizing on international partnerships, and timely entry into the industry; and
- vocal and active participation in international negotiations on trade and benefit sharing, and domestic structures and policy created to protect indigenous resources.

One area of divergence of particular relevance to the present discussion is on the issue of DNA patents; there is no common approach among the three countries on how to address human DNA within patent law.

It is not clear if, and how, the status of DNA as reflected in the patent law of developing countries has affected or may in the future affect the ability of developing countries with relatively strong research and technology bases to harness genetic approaches to improve the health of their populations. It also remains to be seen how these issues will interact with the overall changes to their patent systems as a result of TRIPS coming into force in these countries in 2005.