Bioethical Issues of IPRs

Theme 4 – Breadth of Patent: patents over genetic research tools

Patenting Research Tools in Human Genome Studies: View from a Technologically Proficient Developing Country

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I would like to thank Professor Cornish for inviting me to make a presentation.

This is a paper co-authored by a colleague who has is a practitioner in India, and is currently doing the BCL at Oxford.

In the first section of my presentation I propose a definition of the term 'research tools' as a contribution to the debate on the topic. The definitions we have seen so far have been presented in very general terms, and these may not help in getting a nuanced response from policy making bodies. In the second section of my paper, I will talk about the provisions of the Indian Patent Act, amended in 2000 and 2002 and the relevance of these within the definition of research tools provided in the first section.

The definition of research tools adopted by the Nuffield Bioethics Council, adapted from the 1998 Report of the National Institutes of Health Working Group on Research Tools incorporates two points; one a research tool includes the full range of resources that scientists use in the laboratory, which is not very helpful in itself, and two, it recognises that one firm's end product might be another's research tool. This latter issue is the crux of the problem of patent protection for research tools.

The definition we are proposing here is based on two aspects and draws on the different patents that are being filed. The nature of patents being filed, and the jurisdiction under which they are being filed allows us to elaborate on three categories of research tools in genomics. Research tools we found fall under three broad categories based on their nexus with the final product and the nature of protection from infringement. Richard Nelson, in his paper on basic scientific research proposes that the distinction between applied and basic research is the proximity to the solution of a practical problem or creation of a practical object. This proposition is the basis of our definition and the two factors it incorporates.

Based on a search of the Delphion patent database, there are three sorts of research tools on which patents are being filed; Research Technologies, Research Protocols and Research Hubs. Let me elaborate on these categories:

Research technologies include research tools that can be used in a pan-genomic way to mine data within genomes and by comparing genomes. Many of these are largely bio-informatic in nature as analysis of sequence information requires enormous computational capability, given the quantity of data to be analysed. There is also the obvious question of software

patentability within this category, which I will not go into in detail here. Many of the patent applications filed in this category seem to have very broad process claims. One patent application that illustrates this seeks to restrict the use of information for comparative purposes in order to search for homologies. Research tool patents in this category are also either linked to databases generated as part of the invention or can be used within existing ones. To illustrate, this figure included within a patent application shows an invention that is parasitic on publicly available genome databases.

Certain significant functional parameters further categorise this class of research tools. Recent infringement litigation on a patent that falls within this category took place in the United States. It has already been recognised that United States patent law perhaps has the broadest standards and some research tool patents are likely to be patented only in the US. Given this picture the following litigation throws up some interesting points. One of the key aspects within patents of this kind are process claims, for which it is often difficult to prove infringement. In the following case, US courts have sharply limited the liability for offshore use of the patented research tool.

In the case of *Bayer AG versus vs Housey Pharmaceuticals*, the subject matter of the patent was a genetic screening method to identify proteins of interest; the language was broad enough to cover substances that either inhibit or activate a particular protein of interest that would then affect the characteristics of the cell that produces the protein. Similar screening methods are often used in the search for new anticancer drugs that are toxic to cancerous cells but not to normal cells. This method was patented in the US. Bayer used the method outside the US to identify the a protein of interest which was manufactured outside the United States without further use of the screening method and then imported into the United States.

Normally when a patented process is used outside the territory where there is a valid patent, to produce a product that is then imported back, the act is still infringing. Otherwise the patent protection would not be an effective one. But here the crucial point on which the case turned was whether the screening method could be termed a 'process of manufacture' so that its use, even outside of the United States, would be infringing. Among other things, the court held that the relevant provision only covered methods of actually making or creating a product as opposed to methods of gathering information about, or identifying, a substance worthy of further development.

In the second category of research tools, are included broad procedures or protocols of research; By this I mean research protocols that can be used across different animal models for different biological or therapeutic purposes. What distinguishes this category from the previous one is its relative proximity to the solution of a practical problem. Genetically modified animal models belong to this category.

Prominently, many of the research protocols patent claims include process and product claims. Sometimes, the question of whether the patent application properly describes a product claim or a process claim is not easy to answer as in the case when product claims contain process limitations. This amounts to a description of a product claim in terms of function rather than structure. On the question of infringement of patents, it becomes important to distinguish process and product claims as the scope of protection from infringing acts varies considerably for the two.

The case of *Trustees of Columbia University vs Roche Diagnostics* again involved a case of off-shore infringement. Three patents collectively called the 'Axel patents' cover processes for inserting two genes into host cell (cotransformation) in which one of the genes encode a marker protein and the other encodes a protein of interest. The claims also cover the cell lines produced by the process of amplification and cotransformation. The court was faced with a situation where serum-free EPO, a by-product of the Axel patents was imported in to the United States by Roche, the manufacture of the product having taken place in Germany. In this case, Columbia wanted the court to equate off shore infringing activities with those that take place within the US. However United States law, does not thankfully as yet make extra territorial claims and this outcome was denied in this case.

However, perhaps the more significant aspect of this case is that Columbia sought to use the 'fruits of the poisoned tree doctrine', according to which by-products of infringing acts should also be infringing. The doctrine was originally used in the case of tainted evidence. Where evidence is gathered by the police in an illegal manner the evidence can not be used in court.

The court however, relied on the unequivocal language of the statute that prohibits the importation of patented products and not to the by products that derive from that invention. In this case the serum free EPO, produced using the invention in the Axel patents, was itself not the patented invention as it was not covered by the claims of the patents, but could have been produced using the patented invention. Although the importer was not held liable in this case, if it was proven that the importer used the patented process to manufacture the serum free EPO, then he would be liable under Section 271 (g) of US patent law. The court found therefore that the nexus between the cell line produced and the techniques to produce such cell lines covered by the patent in question was inadequate.

Looking beyond the facts of this case itself, it is often very difficult to prove what processes were used un the manufacture of a particular product, this question of evidence is crucial when it comes to enforcing research tool patents, where by definition the nexus between the subject matter of the patent and the end product need not be immediately obvious.

The third category of research tools is the research hub. In this case, we see prominent product claims in addition to process claims to put the product to use. And again, what distinguishes this from the previous two categories is the relatively greater nexus between

the research tool and the end product obtained from it. Within this category is included genomic information such as ESTs, other partial or full length gene sequences, proteins of as yet unknown function and SNPs (single nucleotide polymorphisms) which are the latest in a long line of genetic markers.

Moving on to the functional parameters for research hubs, in a recent case an antibiotic that was imported into the United States was manufactured outside the United States using an intermediate that was patented in the U.S. This intermediate would fall within the category of research hubs as presented here. The court refused to find that this importation of the antibiotic was an infringing act, because it found the patented intermediate to have been materially altered. The result of this case *Eli Lily and Co v American Cynamide Co* is that when a previously patented product (gene, protein) forms part of another unrelated innovation developed in a place where the original product patent is not valid, importation of this new innovation into the US is permissible, if the original patented product was 'materially changed'. This considerably undercuts the scope of protection offered by a patent on a research hub.

The implications of these off-shore infringements rules for developing countries are significant. It could mean for example that given rules like the one on 'material change' countries like India, could potentially present themselves as safe sites for manufacture of products that are made using patented research hubs that are manufactured for export in a territory where the patent on the research hub is valid. However there is considerable asymmetry in the level of patent protection that can be obtained for some of the research tools described under the three categories here in India as compared to the protection obtainable in the United States. The exact nature of this asymmetry is worth investigating in order to assess whether developing countries present a favourable alternative to the use of patented research tools in manufacturing processes.

Professor Barton in his paper on the implication of patents on research tool for the health of people in developing countries, says that patents on research tools may be a problem for the developed world only. We may never see a problem in the developing countries, as it usually will not make economic sense to file for these patents in developing countries. However a study of the Delphion patent database index shows that there is considerable interest in filing for patents across the range of research tool categories presented today.

A number of such inventions disclosed in patent applications are filed as PCT applications, and specify a large number of developing countries as 'designated countries'. For example, an application for a 'Method to Find Disease-Associated SNPs and Genes', that may be classified as a research technology shows as designated countries, India, a number of OAPI, ARIPO and Eurasian countries. Naming certain countries as 'designated countries' in a PCT application is an expression of interest in filing for patents in such territories subject to a

delayed assessment of whether it makes economic sense to go ahead with a national application. WIPO statistics show that on average national applications are filed in only 40% of the designated countries. It is used here as a measure of potential interest in taking out patents in designated countries.

Interest in filing patents on subject matter that might be called research tools as defined here, has generally increased over the last five years. For example the table here shows a five fold increase in the number of patents being filed to the number of scientific publications on SNPs.

Year	Scientific Paper on SNP	Patenting Relating to SNP Research
2001	1	34.5
2000	1	6.85
1999	1	2.3
1998	1	2.54
1997	1	3.95

Table 1: Decoding the Literature on Genetic Variation; *Coronini et al.* Nature Biotechnology, 2003

This table is derived from scientific data published in January this year. Interestingly, many of the patent applications filed on SNPs are being filed as PCT applications showing a number of developing countries including India and a number of African countries as 'designated countries'. On the basis of this profile of interest in patenting SNP data in developing countries, as well as a study of the patent database index it would be safe to assume that firms in the developed world consider the economic benefits of such patents to justify the costs of filing application. This is so especially in the case of SNPs, markers that that are specifically linked to conditions of disease and therefore that much closer to therapeutic products or processes.

To what extent would it be possible to obtain a patent on such research tool in a country like India? it is generally hoped that an evaluation of patentability made by the PCT governing board handling the examination would lead to more uniform results in connection with the patentability of the invention in each country. And although individual countries are not bound by the determination made during the PCT process, a positive PCT decision on patentability is often persuasive evidence in a national patent office. India has till 2005 to

make her patent laws fully TRIP compliant; in the interim a number of statutory provisions serve to bar patents on many research tool categories.

The most significant limitation on research tool patents, especially of the third category mentioned above, research hubs in India is the distinction between process patents and product patents within certain fields that is maintained until the 1st of January 2005. Patents cannot until that date, be granted for products in the field of agriculture and pharmaceutics and also if the product is the result of a 'chemical process'. The term 'chemical process', has been given a broad meaning in the 2002 amendments of the Indian Patent Act to include biotechnological processes such as a recombinant DNA process. The amendments also clarify that a 'chemical process' includes a 'bio-chemical', 'bio-technological' and 'micro-biological' process. This is a severe limitation on the availability of product patents on research tools.

A range of objections to the patenting of human genomic research tools fall within the general evaluation of subject matter as patentable or unpatentable. One such significant restriction, in the form of a blanket objection to 'life patenting' was recently removed by the Calcutta High Court decision in *Dimminaco AG v. Controller of Patents and Designs & Others (Aid No.1 of 2002)*. The applicant, *Dimminaco AG*, a subsidiary of American Home Products, Inc. had applied for a patent on a process that resulted in the manufacture of a live vaccine, useful as a cure for infectious bursitis in poultry. The application was rejected by the Indian Patent Office on several grounds, the most prominent of which was that the statutory definition of 'manufacture' did not include a process that resulted in a 'living organism'. The Calcutta High Court, in rejecting the findings of the Indian Patent Office, held that the dictionary meaning of the term 'manufacture' did not preclude the inclusion of 'living matter' within its ambit.

Interestingly, the denial of the patent application by the patent office was actually based on an internal circular of the patent office. This internal circular clearly stated that living entities are not patentable under the Patent Act. From this circular, it is clear that there was no bar on processes that involved the use of a 'living organism'[1]; rather the bar sprung into operation only when the end product was a 'living organism'. The circular was not cited as the basis for denial of the application in the first instance, neither was it picked up by the high court for a detailed analysis. Apart from whether the circular interpreted the law correctly, is the issue that the circular was not made known to the public in any sort of way. In this case the high court lost an excellent opportunity to examine the legality of such covert examination practices.

There have been other instances of an institutional rift between the courts and the patent office in India, often resulting in the triumph of a very conservative attitude to patentability

[1] Thus, claims for a process that involved the use of living organisms (such as yeast used in the fermentation of beer) would be permissible.

on the part of the patent office. In one case, the application under consideration disclosed a process that involved the production of a mushroom. The matter was referred to the biotechnology Committee appointed by the Government of India to aid the patent office in making decisions. In an instance of the strong scepticism against life patenting on the part of the patent office, although the Biotech Committee opined in favour of patentability of an inventions that claimed a process involving a mushroom as an end product, the Controller General who had referred the matter to the Committee in the first place disregarded the opinion of the committee and denied a patent.

The rift does not end with governmental committees. On occasion the Indian Patent Office has disregarded the recommendation of a higher judicial body. In a 1980 patent matter, an applicant, whose application related to a method of opacifying a gaseous medium appealed against the outright rejection of his application for which adequate reasons were not assigned by the Patent Office. Although the Delhi High Court seemed to suggest in its decision that such a process would be patentable, even absent an end product, the Controller of patents held when the case had been remanded to him that the Indian patent regime did not permit the patenting of mere processes. The Controller seemed to suggest that he was not bound by the court ruling on this point. These institutional tensions rightly or wrongly tilt the balance against patents on research tools where they encompass broadly conceived 'living matter' as end products.

There are many other provisions within the 2002 amendments of the Act that exemplify the asymmetry in patent protection that will available for genomic research tools in India as compared to the United States. I do not have time to go into detail here, but these include, as presented in the next slide, term of the patent, compulsory licensing provisions, the Bolar exception, burden of proof and the definition of the term 'micro-organisms'. I will deal in detail with one of these, the morality exception.

In most of the literature that deals with patentability of living matter, a central point often raised is the scope of the morality exception. It has been indicated that perhaps developing countries would rely on this exception to a greater extent that have developed countries in recent years. But quite exceptionally we have seen infrequent use of this exception in the Indian context. There is only one unreported instance of the use of this exception. The invention in this case related to medicinal powder prepared from skeletal remains of dead bodies dug up within a week of burial. Digging up graves for profit-oriented purposes was seen as a definite no no by the patent office

One of the reasons why this exception has not gripped the imagination of the patent office in a more expansive way is explained by my next slide. The Indian government has put in place a number of measures to bring in investment into the biotechnology industry to capitalise on

the availability of highly skilled people, and basic infrastructure in the country. A strict or broad interpretation on the morality exception would thwart all of those attempts.

This presentation would be incomplete if I did not go into the public's reaction to advancements in biotechnology. The question of embryonic stem cell research has divided the west sharply. But remarkably enough, this has turned out to be an apolitical issue in India. Recently, as you may be aware the Bush administration decided to cut back on federal government funding for the development of new embryonic stem cell lines, and decided instead to include laboratories that had these cell lines as potential collaborators on applications for funds. This has put two Indian laboratories, one in the public sector and the other in the private, on the embryonic stem cell research map; between them they have developed 9 cell lines. This was received by the public by and large as a positive symbol of desirable technological progress in the country. For the last few decades, subsequent governments have facilitated population control measures; because of this, the question of medical terminations of pregnancy does not divide people as it does in many developed countries. To a large extent abortion is an apolitical issue in India. This has made it easier to accept research on embryonic stem cells. The Indian Government has drafted guidelines on the matter that approves of ethically conducted embryonic stem cell research, and human cloning is prohibited.

Another interesting reaction has come from a senior scientist and I dare say is shared by some sections of the populations. He described in detail his reasons for believing that this technology was in fact one of the lost sciences of India. The alleged description originates in the epic Mahabharat, which describes the birth of 100 princes from a hard ball of flesh. These sort of claims oddly enough could bolster a general optimism with respect to biotechnology.

However, there have been other reactions as well from orthodox Hindu pontiffs. Like anti-abortion groups in the United States, they believe life begins at conception and scientific tinkering with embryonic cells is wrong. Shankaracharya Jayendra Saraswat, one of the five leading Hindu pontiffs in India, said in a written statement. 'Abortion, artificial insemination or even test tube babies are sinful acts and are not acceptable'. Such views are, however, in a decided minority here. India is a poor nation of more than 1 billion people, where the need for containing the alarming rise in population outweighs religious scruples on such issues as abortion, which has always been legal.

This brings me to the concluding slide. I have two conclusions to make today, the first is a submission of a new categorisation of research tools, that is necessary if we hope to elicit a nuanced response from the patent system. The second, slightly provocative conclusion, is that the asymmetry in patent protection in most developing countries coupled with the fact that such research tool patents are being granted in developed countries could well mean that companies find developing countries to be attractive sites of R & D and manufacture.

This could well be a good idea for budding biotechnology industries in many developing countries.

Thank you.