

Patents in a genetic age

The present patent system risks becoming a barrier to medical progress.

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and Sandy Thomas**

In helping to develop many discoveries into clinically useful products, the patent system has been a force for good. It has encouraged innovation and sensible risk taking, stimulated investment in research and development, and delivered drugs and devices that have changed the face of modern medicine.

But can the patent system maintain this positive influence in the future? As we stand on the brink of one of biomedical science's greatest achievements — the complete sequencing of the human genome — this question becomes extremely pertinent. The issue of how and when to assign patent rights to all manner of DNA sequences threatens to throw the patent system into disarray.

The patenting system should help people to channel their energy towards inventions of genuine therapeutic or diagnostic value and discourage the frenetic cataloguing of DNA sequences that are a long way from being a final, useful product. But as it stands, the system is in danger of not fulfilling these functions. It can be slow, and prohibitively expensive to navigate. Moreover, patenting is increasingly being seen by some as rewarding luck rather than enterprise.

Retuning

The present state of affairs is partly a result of the way the patent system has evolved in recent years. It has changed from focusing on conventional drugs to being a system that also encompasses patents on biological molecules containing genetic information (see Box, overleaf). Many thousands of patents with claims to human DNA sequences have been filed and granted¹, and few have as yet been subject to legal challenge. The many patents include claims for genomic DNA sequences, complementary DNAs, individual mutations, expressed sequence tags (ESTs) and single nucleotide polymorphisms (SNPs; see glossary on page 815). Unless the system is retuned, there is a serious risk that complexity will heap upon complexity, making it unmanageable.

Will these patented sequences actually be used to develop new healthcare products, and if so, how? Some already have been — for example, in the gene-based diagnostic tests for cystic fibrosis and breast cancer. But the granting of exclusive property rights for disease genes so that they are under the sole control of the patent holder has already generated wide debate about whether claims



Debate continues over whether DNA sequences can be claimed to be part of an invention.

to DNA sequences as part of an invention can continue to be justified.

Many gene patents are also being filed for their potential, though unpredictable, role in drug development. But apart from in rare situations, it is generally the protein products, their derivatives and antagonists, rather than the encoding DNA, that will bring medical benefits. Proteins, and even parts of proteins — characteristic arrangements of molecules (motifs), folds and subsections — are already subject to the same welter of patent claim and counter-claim as DNA sequences. For example, one US patent² covers a computer-assisted method for identifying compounds possessing a similar structure to the hormone erythropoietin. Anyone using the three-dimensional coordinates to identify crystal structures similar to a specified peptide might infringe the patent³.

In the human body, the components of the functional genetic units — exons, SNPs, mutations, protein motifs, control regions and transcripts — are all integral parts of the same biological mechanism that interacts with other gene products. If the DNA sequences of all of these components are identified and then treated as separate 'inventions', any useful product is highly likely to cross the boundaries of several patents. The ensuing accumulation, or 'stacking', of patents⁴ on a product requiring licences would be lucrative for lawyers, and profitable

for the few people fortunate enough to have rights to the key elements of genetic information. But it is hard to see it as a defensible means of rapidly developing cost-effective and useful products.

Claims that such problems will not occur, because the patent system is self-correcting through legal challenges, do not stand up to scrutiny. A legal challenge is generally slow and expensive, and its outcome is unpredictable. Moreover, patent holders from academia and small companies are particularly disadvantaged. Long and expensive litigation, and conflicting judgements on what should be patented, are not a sensible way forward in such an important and fast-moving area. Furthermore, although many patent claims to human DNA sequence may well eventually fail under legal challenge, until they do they are an expensive barrier to progress in applying the fruits of medical research to clinical and therapeutic practice.

Policy failures

Who are the villains of the piece? Not the scientists, nor the individuals in business — they are playing within the rules. Nor the lawyers, who are appropriately pursuing their clients' interests. Nor is it the understaffed patent offices, which are under constant pressure from well-resourced proponents. We suggest that it is the lack of leadership from policy-makers that has allowed the present state of affairs to come about. Our elected representatives — put off, no doubt, by the complexities of the patent system, strong vested interests, and a reluctance to address the international dimension — have failed to develop public policies for biotechnology that address the weaknesses of the patent system yet retain its strengths.

In the absence of serious legislative action, policy has more or less evolved through dialogue within a limited circle of participants. Commercial interests, which are well represented to the patent offices, have not been counter-balanced by those who represent the broader public interest. The result has been an innate tendency for the patent system to 'creep' in the direction of extending patentability to biotechnology inventions for which the thresholds for novelty, inventiveness and utility have been lowered.

Legal challenges from other parties can redress the balance of interests, but this route is often eschewed by the private sector in favour of individual licensing deals — it is often quicker and less expensive to arrange a cross-licensing agreement than to challenge

a claim in court. And there has been remarkably little assessment by elected representatives of whether the system's current balance is likely to serve the public interest.

The fact that policy-makers have done little to reform the patent system is surprising given the importance of patenting in health-care. Why is this? Policy has broadly evolved at four levels: through international agreements such as the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS); through regional and national legislation such as the Directive on the Protection of Biotechnological Inventions from the European Union (EU); through the patent offices; and through the courts. The main failing of this set of institutional arrangements is that it has not produced a coherent policy framework. Instead, the attention of policy-makers has been uneven and there have been few attempts to grapple with the patent system as a whole.

TRIPS contains no explicit reference to genetic material. In the EU, policy has been dominated by the protracted passage of the directive; and the legislation, passed in 1998, did little more than formalize current practice. Although the Netherlands has since challenged the directive in the EU Court of Justice in Luxembourg on procedural grounds, it is unclear where this action will lead.

In the United States, industrial lobbies have been influential in Congress and the Senate in maintaining what is essentially a pro-patent, liberal policy-framework for biotechnology. But there have been some recent welcome adjustments. For example, in response to the debate about the patentability of ESTs, the US Patent and Trademark Office has tightened up its utility requirement⁵.

Targets for reform

What more could policy-makers be doing to address these patenting issues? Reforming the patent system would undoubtedly be politically complex, particularly if it included attempts to achieve international agreement. But that is no reason not to try. The legal and managerial complexities of the current framework risk slowing progress, which is not in the interests of the vast majority of the world's population.

As a first step, there needs to be a clear articulation and discussion of the key questions: whether patents on DNA sequences can continue to be justified in the context of current technology; whether such patents are actually necessary for successful innovation in healthcare; what the thresholds should be for novelty, inventiveness and utility; and what the duties of patent holders should be in licensing their inventions. There is also an urgent need to obtain evidence that might help in evaluating how current and future practices may affect healthcare inno-

To patent or not to patent

The general principle of the patent system is that it protects an invention from commercial competition. An inventor is granted a time-limited monopoly to exploit an invention if it is shown to be new, not obvious, with a useful application, and is disclosed in sufficient detail to allow verification. When applied, for example, to machine parts, this process is relatively straightforward. But when applied to conventional drug development, compromises are necessary. Although some drugs are genuine inventions, designed and synthesized by human ingenuity, others are based on naturally occurring, pharmacologically active molecules. It could then be claimed that these are discoveries rather than inventions. But it is widely accepted that this class of drugs also warrants patent protection because the steps involved in extracting, isolating and purifying these molecules from their natural state to one of pharmacological utility are sufficiently inventive to warrant a reward for success.

But future drug discovery, as well as diagnostics and novel therapies such as gene therapy, will increasingly depend on genomic information. To a degree, the patent system has been adapted to cover gene sequences and related matters. But although patent law now recognizes the patentability of DNA sequences, this may be one of those uncommon instances in which the law has lost touch with the way the real world works.

Although many patentable inventions might lie along the road towards developing useful products from the genetic information encoded in DNA sequences, the starting point — the normal or abnormal naturally occurring gene sequence — is the isolation of naturally occurring information. The argument, which has been widely used by patent lawyers, that DNA sequence identification is a form of purification "outside the body", analogous to the purification of naturally occurring pharmacological agents, appears specious. The DNA molecule is not (in this context) important as a substance. Its value resides in its information content — knowledge, not objects.

Similar arguments have been put forward for patenting complementary DNA sequences (cDNA): the 'natural' gene contains introns — sequences of DNA that are not translated into the final protein — and so synthesizing a cDNA is an 'alteration' of nature and as such a human invention. But this, too, seems intellectually trivial. Messenger RNA exists in nature, and cDNA is just a translation of this sequence. This is rather like saying that the same invention could be repatented if translated into a different language.

Finally, there should be an objective assessment of the efficiency of the current frameworks — including the patent offices, courts and legislative bodies — in determining policy.

Clearly, these issues need to be addressed in an international policy forum, perhaps within the ambit of bodies such as the World Intellectual Property Organization or the World Health Organization. Alternatively, a new body might be created. But for all the talk of international harmonization, patents remain essentially national in nature. The US, European and Japanese jurisdictions would have to be considered separately. It is already late in the day to be contemplating an international policy forum given the rapid growth in the fields of functional genomics, structural genomics and proteomics. To be of any use, such a forum must be able to influence policy-makers. And it should be set up without delay.

In arguing for change, we acknowledge that the patent system has, on the whole, worked well. But it has now moved into very different territory without appropriate policy guidance. The system does not need a complete overhaul. But it does need more than tinkering. In particular, it needs to adjust the stringency of the definitions of inventiveness and utility required for a patent⁶. Rigorous attention to such detail could greatly improve the system without altering its fundamental role in innovation.

We stand on the brink of biomedical science's greatest achievements. To make full use of them, we need the enthusiastic sup-

port and backing of the world's population. The grim signpost of genetically modified foods in Europe should remind us not to underestimate the power of public opinion. Epithets such as 'land grab' abound in press comments, on both sides of the Atlantic, on the recent spate of patents filed on parts of the human genome. The analogy is not misplaced. It has been a rush, and luck has often played a major part in determining which particular group gains the intellectual property rights over its competitors.

The human genome sequence is finite whereas human inventiveness is infinite. Public perception of scientists as being motivated by short-term financial gain is not only unfair to virtually all scientists, but also risks bringing biomedical science into public suspicion and disrepute, at a particularly sensitive time in its evolution. We can ill afford this risk. ■

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