

Current problems with the patenting and licensing of prescription drugs

This submission has been written at short notice, as we only came to hear of the Gowers Review by chance and just before the deadline. We would be willing to supply further information. We have no commercial interest in, or specialist knowledge of, Intellectual Property law. We are however well placed to comment on the operation of the law as it applies to the patenting of prescription drugs, from the perspective of academics with interests in drug safety and genuine innovation in the pharmaceutical industry. There are 3 related problems we would like to describe and propose solutions to.

Problem 1: Drug safety

The current patent laws grant a protected period of 20 years from the registration of a new molecule. During that period, the pharmaceutical or other company developing the drug has to go through a number of stages before the drug can be licensed by the Medicines and Health related products Regulatory Agency (MHRA) (formerly the Medicines Control Agency). These include laboratory tests; animal tests; testing in healthy volunteers (phase 1 trials); preliminary testing in relevant patient groups (phase 2 trials); and testing in larger patient populations (phase 3 trials). Data from these developmental stages are submitted to the MHRA with the licence application. Once the drug is licensed, the company has a limited time (20 years minus the time spent on development) in which it can exclusively exploit the drug before its competitors are allowed to manufacture it generically.

Clearly the financial pressures on pharmaceutical companies (to obtain a return on their research and development costs) provide a powerful incentive to minimise the time taken on development and to maximise the time spent on exploitation before the patent runs out. The current system therefore gives the companies few incentives to make proper assessments of the safety of new drugs. The main incentives are the requirements of the MHRA at the point of licensing. It could be argued that these are a disincentive to assess safety properly, since a) the requirements are a minimum, b) too much information about adverse reactions (side effects) might jeopardise a licence application.

At the point of licensing, a new drug will have been tested on a comparatively small population. By definition, any rare side effects will probably not have been detected. In the first few years post-licensing, the drug will be prescribed to a far greater range of people, and many more, than it was tested on, some of whom will experience side effects. So-called post marketing surveillance studies (phase IV trials) have been supposed to capture data on these side effects, but they are often merely marketing exercises by pharmaceutical companies aiming to familiarise doctors with the product and maximise prescribing rates. In the worst case scenario (e.g. the recent problems with Vioxx, a COX 2 inhibitor), the drug will be widely prescribed, some people suffer adverse effects including death, the problem eventually comes to light, and the drug is then withdrawn. In a less extreme scenario, the side effects are less serious, and the connection between the drug and the side effect comes to light much more slowly. These “less serious” side effects may however cause distress and reduced quality of life for the people experiencing them.

To summarise: the current arrangements for patenting and licensing prescription medicines provide a poor basis for establishing the safety record of new drugs.

Our proposed solution would require changes to both the patenting and licensing arrangements which we see as inextricably linked. We propose that the licensing of a new drug should be provisional, for say a two year period. During that time, the

pharmaceutical company would be expected to perform detailed clinical studies of any adverse effects of their product, including Prescription-Event Monitoring studies (in which physicians follow up all their patients prescribed the drug for a year afterwards, recording all events reported by patients), and genuine phase IV trials aimed at providing robust epidemiological data on its safety. At the end of the two years, the company would apply for a full licence, providing the MHRA with complete safety data. If the MHRA was satisfied with the quality and results of these data, it would grant a full licence as well as an extension of the patent, for a fixed duration of say 10-15 years. In this way, the safety profiles of new drugs would be more robust, and companies marketing safer drugs would be rewarded with an extension of their patent.

Problem 2: The term 'innovation' and its relationship to patents

The term 'innovation' covers three concepts:

- the commercial concept - any *newly marketed* me-too product, new substances, new formulations, new treatment methods;
- the technology concept - any *industrial innovation*, such as use of biotechnology, use of a new substance delivery system (patch, spray, etc), selection of an isomer;
- the concept of *therapeutic advance* - a new treatment that benefits patients when compared to previously existing treatments.

As we understand it, patents are granted for inventions shown to be or do something new, i.e. distinct from what already exists. These are covered by the first two categories above; the idea of 'therapeutic advance' appears to have no separate role in the granting of patents.

This is unsurprising, since patents are granted to protect inventions that have potential commercial value. The potential benefit (or harm) of an invention to society does not influence whether a patent is granted or not. The underlying assumption is that the market will determine how society values the invention. The patent owner is given exclusive rights to exploit it for a fixed term, and therefore does their utmost to establish its reputation and maximise sales within that period.

In the case of pharmaceuticals the market cannot value an invention correctly, mainly because this requires (1) much information about its nature and effects that the patent holder does not disclose, (2) specialised resources and skills.

The laws and regulations for licensing medicines have complicated this problem but not solved it.

The attached *ISDB Declaration on therapeutic advance in the use of medicines* examines the implications for public policy.

Problem 3: 'Evergreening'

A separate issue for the rules that govern drug patenting concerns a practice called '**evergreening**'. It has become common in the pharmaceutical industry for companies to replace successful products whose patent is nearing expiry with a slightly different one that has the same effect, but can be claimed to be an improvement. This may be a slightly different molecule, or a different formulation of the old drug with slower or faster release of the active ingredient, or made by a different ("better" or cheaper) manufacturing process, or combined in the same tablet with another substance that is supposed to improve the properties of the medicine.

On expiry of the first patent the company stops promoting the original product, often then marketing the new product at a lower price to make the old one unattractive.

The replacement of effective and successful racemic drugs (which are 50:50 mixtures of two optical isomers) is a prominent example, with the argument that the inactive isomer has been removed, so that its undesired effects are eliminated - although it may not have been shown to do any harm. Examples include the replacement of omeprazole (inhibitor of gastric acid secretion) by esoprazole, loratadine (antihistamine) by desloratadine, citalopram (antidepressant) by escitalopram. The replacements offer no real therapeutic advance, but they have been heavily and successfully promoted; they have cost patients and health services enormous sums, essentially wasted. They are basically a trick for gaining a further term of patent life for the same treatment: the 'innovation' is purely technical, not therapeutic.

To award patents for such medically pointless innovations encourages trivial research and deprives society of resources that could and should be used to develop needed innovations. In this respect current patent law demeans the concept 'intellectual property' by confusing it with intellectual impropriety.

We propose that patents be issued provisionally, and granted in full only if significant therapeutic value *in comparison with other treatments* has been proved within a stated period, e.g. 6 years. The length of this period would have to depend on the purpose of the drug: if therapeutic value can be shown in weeks or months, it will necessarily be shorter than if therapeutic trials will take several years.

Professor N Britten, Peninsula Medical School, Universities of Exeter and Plymouth

Dr A Herxheimer, Emeritus Fellow, UK Cochrane Centre, Oxford

References

M Mitka, Accelerated approval scrutinized: confirmatory phase 4 studies on new drugs languish, *Journal of the American Medical Association*, 25 June 2003, p 3227.

B Kermode-Scott, Agencies 'failed miserably' over COX 2 inhibitor, *British Medical Journal*, 15 January 2005, p 113.

International Society of Drug Bulletins. *ISDB Declaration on therapeutic advance in the use of medicines*. Paris: ISDB, November 2001.