InFocus
Unlicensed and off-label use of medicines in the UK - A balancing act

The Background
In general, it is illegal to sell a medicine in the UK unless it has a marketing authorisation. Marketing authorisations for the UK can be issued by the Medicines and Healthcare products Regulatory Agency ("MHRA") or the European Medicines Agency. Regardless of the authorising body used, a marketing authorisation will only be granted for a medicine that has been assessed as meeting the required standards of safety, quality and efficacy. The assessment of efficacy is in relation to at least one named indication, and the company applying for the marketing authorisation ("MA") must provide clinical data demonstrating such efficacy. Demonstrating efficacy for more than one indication will usually require additional clinical studies at significant associated expense. Therefore, it is common for a MA to be sought for the one indication that provides the biggest market for the medicine. The label used in connection with an authorised medicine will state the indication for which the medicine is authorised and any other restrictions, such as age limits of the target population.

All medicines that have been granted a MA can be referred to as licensed. However, a licensed medicine may be useful for indications or in populations (such as children) in addition to those stated on the label. Any use of the medicine for indications or in populations not stated on the label is referred to as an off-label use through necessity (for example, where the medicine has not been tested in children but there is no licensed alternative) or become apparent through the accumulation of experience and data relating to the medicine and similar medicines. In any event, the safety and efficacy of the off-label use has not been assessed by an authorising body and therefore, arguably, presents higher risks for the patient. However, healthcare professionals will weigh the risks and benefits of prescribing an unlicensed medicine or an off-label use of a medicine for a particular patient. In doing so, healthcare professionals in the National Health Service ("NHS") have a duty to make the best use of public resources: cost as well as clinical suitability and product quality are required to be considered when choosing appropriate treatments.

View from the NHS
The NHS has a limited pot of money for use in purchasing from an almost unlimited number of treatment options. Off-label prescribing by healthcare professionals has the potential to provide cheaper access to medicines for the NHS, partly because many medicines that could be beneficially used outside of their licensed indications are older medicines without patent protection.

The National Institute for Health and Clinical Excellence ("NICE") is a non-departmental public body funded by the Department of Health, whose role is to help ensure that NHS funds are well spent. It evaluates medicines and other medical treatments and produces evidence-based guidance for use by the NHS as to which treatments provide the best quality of care and value for money. NICE recommendations, although not binding on health professions (who are free to make their own decisions regarding treatment of patients), are expected to be taken into account. Where a medicine has been recommended by NICE, Primary Care Trusts ("PCTs") are required to fund its use by the categories of patients specified by NICE. Where a medicine has not received NICE approval, it is available at the patient’s (or insurer’s) cost, or at the discretion of the local PCT. Each PCT must balance their budget against the varying needs of patients, which can create differences in the treatments that various PCT’s are prepared to fund.
NICE does not issue guidance on the use of a medicine until after it has been granted a MA and will not appraise a medicine outside of its licensed indication. In a departure from this traditional role, in October 2011, NICE announced that it would provide advice on the use, in special circumstances, of unlicensed and off-label uses of medicines. This advice will not be formal guidance but is intended to be a summary of the available evidence to inform decision-making by healthcare professionals. NICE will not provide a “yes” or “no” recommendation on the use of unlicensed or off-label medicines. In May 2012, NICE advised that it expected the first such evidence summary to be issued in the summer of this year.

View from the GMC  
(Guidance to Doctors)

The General Medical Council (“GMC”) is the independent regulator for doctors in the UK, whose purpose is to protect, promote and maintain the health and safety of the public by ensuring proper standards in the practice of medicine. Part of the statutory role of the GMC is to provide guidance to doctors on medical ethics. The GMC requires doctors to comply with the standards of good practice set out in guidance published by the Council.

The most recent guidance on prescribing medicines, including unlicensed and off-label medicines, was issued in September 2008. The current guidance provides that doctors:

i) may prescribe unlicensed medicines but must be satisfied that an alternative, licensed medicine would not meet the patient’s needs; and

ii) may prescribe medicines for purposes for which they are not licensed (off-label) but must be satisfied that it would better serve the patient’s needs than an appropriately licensed alternative.

In both cases, the doctor must be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy.

In 2011, the GMC held a consultation on an update to that guidance. The draft revised guidance provided that doctors must usually prescribe licensed medicines for their licensed uses, but may prescribe off-label or unlicensed medicines if there is no appropriately licensed alternative available or the doctor is satisfied, on the basis of authoritative clinical guidance, that it is as safe and effective as an appropriately licensed alternative. Thus, the draft revised guidance provided more freedom to doctors to prescribe unlicensed or off-label medicines.

The GMC consultation asked for feedback on this broadened scope. 70% of the respondents supported the proposed changes (with 20% disagreeing and 10% not sure). However, notably, the MHRA and the Association of the British Pharmaceutical Industry opposed the change. As a result of their concerns, the GMC obtained legal advice on the relevant provisions of the EU Directive on medicinal products for human use. On the use of unlicensed medicines, the advice confirmed that they could be prescribed only where there was a ‘special need’ and this did not include use where there was a licensed alternative (whether or not publicly funded). As a result, the GMC has stated that it intends to revert to its existing guidance on use of unlicensed medicines. In relation to the use of medicines off-label, this is not explicitly covered by the EU Directive and the GMC has advised that it is seeking further advice. The revised guidance is expected to be published in September 2012.

View from the Pharmaceutical Industry

In early May 2012, the Association of the British Pharmaceutical Industry (“ABPI”) issued a press release stating that the “health and safety of UK patients should always be paramount, and all other considerations, including cost, must be secondary.” In the statement, the ABPI reiterated that use of unlicensed medicines put patients at risk and should be strictly limited to those occasions where there is no licensed alternative. The ABPI did not explicitly refer to the Lucentis / Avastin case but did refer to the risk introduced where medicines used off-label are reconstituted and delivered to the patient in a different way than originally intended. The same arguments against use of unlicensed and off-label medicines have also been taken up by the European Alliance for Access to Safe Medicines, a patient safety campaigning group backed by the pharmaceutical industry.
A further argument advanced by the pharmaceutical industry against use of unlicensed and off-label medicines is that this use creates a disincentive for pharmaceutical companies to undertake the significant and expensive work required to obtain a MA for a new medicine. This argument highlights the balance that must be created by policy makers between providing cost-effective healthcare and incentivising innovators by enabling them to recoup their investment into the research and development of new therapies. Patent protection and regulatory exclusivity have been the traditional means of enabling innovators to protect their investment, but if policy makers diminish this protection by endorsing ways of “working around” the established regulatory system, innovators will be forced to challenge this endorsement or create new barriers to the use of generic medicines.

The impact of patents

As discussed in our article “Patent infringement in the UK and Europe - usage patents, carve-outs, skinny labelling and off-label prescribing”1, when patent protection for a medicine expires, it is common for certain uses of the medicine to remain independently patented. Thus, the medicine itself can be manufactured without patent infringement but cannot be used for the patented uses. One approach used by generics companies to avoid infringement of such use patents is to ensure that the labelling for the generic product does not refer to the patented use. However, the effectiveness of this method in avoiding patent infringement is largely untested in the UK and Europe. The practice appears to have been derived from the US. However, US law differs significantly from that in Europe, and requires generics companies to certify that they will not market a drug for patented uses.

Clearly, where a generic medicine is marketed for uses other than patented uses and at a significantly lower price than the patented medicine, there will be a temptation to prescribe the generic medicine off-label for the patented uses. Although, the use of an abbreviated label on the generic product may enable the generic company to avoid patent infringement, it ignores the commercial reality. We expect that it will not be long before this “non-infringement” theory is tested in the courts.

Where do we go from here?

Unfortunately for innovative pharmaceutical companies, most signs seem to be pointing towards the increased use of unlicensed and off-label medicines. We will be following the progress of the recent Novartis case closely as it has the potential to either speed up this trend - in the event of a decision in favour of the PCTs - or cause a significant re-evaluation by the NHS, NICE, and possibly the GMC in the event of a decision in favour of Novartis. Furthermore, it is only a matter of time before the use of an abbreviated label on a generic medicine to avoid patent infringement is challenged. The pharmaceutical industry will continue to seek new ways of protecting its investment in innovative medicines and governments must carefully balance immediate cost savings against long term innovation and scientific progress. Where governments do not achieve this balance, the courts may step in to the extent they are able, to interpret patent law to ensure it achieves its intended purpose.