Introduction

In July 2013 Pinsent Masons ran a seminar on ‘Adaptive Licensing’ with no less a personage than Sir Alasdair Breckenridge, ex-Chairman of the MHRA, as the keynote speaker. It attracted a high quality audience who participated enthusiastically, but it was clear from discussions with clients and others that the issue was yet to grab the attention of the pharmaceutical industry executive ‘on the street’. However, in the intervening months it has become a hot topic. Particularly for medicines in areas of high unmet need, there is a growing impetus behind both facilitating early access to unlicensed medicines and speeding up the licensing process. The hurdles imposed upon smaller companies by the costs of Phase III trials and the fitness for purpose of the entire regulatory regime for personalised medicines, stratified patient groups and rarer diseases are increasingly questioned.

Existing National Routes

There is considerable flexibility under EU legislation as to how Member States can permit use of medicines without (or outside) a marketing authorisation for specific patients where the health professional considers that the benefits for that patient outweigh the risks. EU medicines legislation largely gives Member States wide discretion as to the procedures under which unlicensed products can be made available to patients. ‘Managed Access Programme’ (MAP) is an increasingly common umbrella term used when defining an ethical solutions-based approach to provision of ‘unapproved’ medicines for patients with unmet medical needs. Currently in Europe, national unlicensed routes to market include compassionate use to meet the needs of a group of patients, use on a named-patient basis, the use of an authorised product outside its authorised indication (off-label), and the individual importation of products for personal use authorised abroad but not in the country of importation.

The United Kingdom has consulted on an Early Access to Medicines Scheme for highly promising medicines in areas of high unmet need, and this initiative was endorsed and encouraged in the September 2013 Report of the Expert Group on innovation in the regulation of healthcare (‘the Report’). The particular perceived gap in regulatory practice was for pre-approval use of medicines for life-threatening, chronic or seriously debilitating conditions without adequate treatment options that had completed Phase III, or exceptionally Phase II, trials. The scheme finally saw the light of day on 14 March with the announcement of a ‘breakthrough’ type designation which could afford the holder both regulatory and reimbursement benefits but requires free of charge supply whilst unlicensed. The new scheme opened to applicants on 7 April.

Existing European Early Licensed Routes

The EU medicinal product harmonised regulatory framework is more proscriptive as to the licensing requirements, but, given the length of time it would take to change EU legislation, the European Medicines Agency has taken up the challenge to examine ways
to expedite market entry within the existing restraints. The MHRA has declared itself a supporter of the ‘adaptive licensing’ movement and was tasked with developing a pilot programme for adaptive licensing. There is a shared view that the existing routes to early licensing – most commonly either by way of conditional approvals or as a consequence of ‘exceptional circumstances’ – may not be being interpreted sufficiently pragmatically or are being underutilised by potential applicants. The Expert Group reported that there had only been 12 conditional approvals granted and 25 licences granted under exceptional circumstances between 2007 and the date of its review.

By a quirk of fate the EMA’s adaptive licensing pilot project was launched within days of the UK’s initiative with some retrospective case studies and a call for applicants to go through the ‘live’ process. ‘Adaptive licensing’ has been defined by the EMA as ‘a prospectively planned, adaptive approach to regulation of drugs ... through iterative phases of evidence gathering, followed by evidence gathering and licence adaptation ... to maximise the positive impact of new drugs on public health by balancing timely access for patients with the need to provide adequate evolving information on benefits and harms’. The idea would be to focus initially on a population of good responders, followed by adaptation of the licensing conditions as more evidence becomes available.

**Early Licensing: EU/US Comparison**

The Report also addresses the international context and compares the EU assessment and regulatory possibilities for early licensing with the FDA breakthrough designation and other US methods of accelerated approval. In broad terms, the following methods were considered comparable:

- conditional approval and approval under exceptional circumstances (EU) and accelerated approval (US) for serious or life-threatening conditions or rare conditions – the former allowing approval on lesser data, the latter on an effect observed in a surrogate endpoint reasonably likely to predict clinical benefit;
- accelerated assessment (EU) and priority review (US) – the former shortening CHMP opinion time from 210 to 150 days, the latter reducing regulatory review from ten to six months;
- fast-track designation mechanisms in both jurisdictions, offering greater regulatory authority support and interaction;
- orphan designation procedures in both jurisdictions, offering variable degrees of support;
- while US breakthrough designation affording expedited development and review with more FDA support has no direct EU equivalent, similar supportive mechanisms are available in the EU.

While the opportunities might equate, there is a recognition and concern that such accelerated methods were less frequently used in the EU than in the United States.
Accelerated Approval and Exclusivity

An issue that has arisen is the extent to which an EU conditional authorisation comprises entry into the market for the purposes of the supplementary protection certificate (‘SPC’) regime.

In Case 617/12 AstraZeneca, the Court of Justice of the European Union (CJEU) decided that AstraZeneca had to use its Swiss authorisation as the first date of authorisation in relation to the lifetime of its SPC. The court said that even though the authorisation given in Switzerland was conditional, the company was able to sell Iressa (the drug in question) in both Liechtenstein and Switzerland, therefore that date is the point from which the term of the SPC should be calculated.

There has also been a case before the CJEU in relation to provisional marketing authorisations for a plant protection product and whether they qualify as marketing authorisation under those regulations. It was held it did. The conditional marketing authorisation for a medicinal product is arguably not an equivalent to a plant protection provisional marketing authorisation for products, but, again arguably, they may be considered on their face to be marketing authorisations that qualify under Article 3(b) of the medicinal products SPC Regulation 469/2009. However, this is an open area and under the current regime the benefits of an early launch may be overcome by the potential loss of exclusivity at the end of the SPC period.

Whether a conditional licence triggers the commencement of a regulatory data protection period is also potentially at issue.

The Broader Perspective

A critical factor in any adaptive licensing initiative will be the response and attitude of payers to a product that has gone done this route. In March 2010, there was a proposal for joint meetings between the MHRA and NICE (the National Institute for Health and Clinical Excellence). Only one such meeting has taken place to date. Given that any accelerated licensing programme would be valueless if the new medicines in question were not paid for, it is vital that the two agree an approach to the pricing and reimbursement of such products. A possible solution may be managed entry agreements under which a manufacturer and a payer or provider establishes specific conditions for reimbursement of a medicine. These can be a useful stepping stone towards the development of new pricing and reimbursement models.

‘Big Data’ will also have a critical part to play. The Clinical Practice Research Database – the UK primary care database comprising data from 5 million patients – is an example. Use of such databases will be a key part of optimising stratified product commercialisation and managing pharmacovigilance and the post-marketing trial requirements that companies are likely to face. This was due to go live in April 2014 but has been delayed six months due to lack of public awareness.
Conclusions

With any change in the core EU medicinal product regulatory regime either for early access or for accelerated licensing seemingly not on the cards, there will need to be a degree of pragmatism both on the part of regulators and producers. The education of companies who have not historically used the existing flexibilities will be the initial priority and thereafter both sides will need to be creative in their application of existing rules using a risk-based approach. A successful experience might hopefully translate into a future revision of EU medicines legislation.

The potential consequences from this reappraisal of risk, benefit and investment for patients, industry and public health are many. Further consequences of adaptive licensing may well include a re-appreciation by potential investors and big pharma licensees in life sciences technology as to development risks where they can see earlier marketing potential. In addition to an increased willingness to invest, the increased use of accelerated licensing may well lead to changes in milestone/royalty structures and in the parties’ respective roles and responsibilities in development agreements and similar collaborations in terms of managing the development process.