Adaptive licensing and its basis under the current EU regulatory regime

Paul Ranson and Helen Cline examine how the new EU adaptive licensing proposals could be implemented under the existing laws and the extent to which any subsequent legal revision might reflect these proposals.

The full development process for an innovative medicinal product can take up to between 12 and 15 years at a typical cost of over £1 billion ($1.7 billion). In response to patient and public pressure and, in particular, the HIV/AIDS crisis in the 80s and early 90s, significant steps were made towards making experimental drugs intended to treat life-threatening diseases more widely available to severely ill patients and speeding up the review and approval of the applications for these products. This pressure continues today.

Recently, both the European Medicines Agency and the US Food and Drug Administration have demonstrated a real willingness to innovate to extend this process. Thus far, the FDA has introduced its “fast track designation” and more recently its “breakthrough therapy designation” for drugs demonstrating a substantial improvement over existing therapies. Like the US, the EU has introduced regulatory mechanisms for early unlicensed access and expediting drug review and approval, including the conditional approval pathway. As yet, the EU has no measure in place that is comparable to the FDA’s breakthrough designation. However, the EMA is introducing the concept of “adaptive licensing” and in March it announced plans to test the procedure in a pilot project. It has been implicit in these proposals that any such scheme would necessarily need to be within the current legal regime. In this article, therefore, we look at how the new adaptive licensing proposals could be implemented under the existing laws and the extent to which any subsequent legal revision might reflect these proposals.

The proposals

In March 2014 the EMA launched the program, inviting companies to participate in its adaptive licensing pilot project. Companies interested in participating in the pilot were requested to submit ongoing medicine development programs for consideration as prospective pilot cases.

The principles of adaptive licensing are now widely known even if the details are sketchy. It is intended to be a prospectively planned process, starting with the early authorization of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorization (MA) to expand access to the medicine to broader patient populations.

Whilst the existing legal framework and routes described in this article will be the bases of the new approach, supporters are asking prospective stakeholders with a role in discussing and determining patient access, including the regulatory authorities, the applicant, HTA bodies, clinicians and patient organizations, to adopt a new collaborative “mindset” in implementing the existing laws. It is proposed that the discussions would take place in a “safe harbor” environment to allow free exploration of the strengths and weaknesses of all options for development, assessment, licensing, reimbursement, monitoring, and utilization pathways in a confidential manner and without commitment from either side.

EU regulatory background

In the EU, the regulatory process for medicinal products is set out in Directive 2001/83 and Regulation 726/2004 (for centrally approved products). With a few very limited exceptions, no medicinal product may be placed on the market in the EU unless an MA has been issued. An application for an MA must be accompanied by specified particulars and documents, submitted in accordance with Annex I to Directive 2001/83 including:
- results of pharmaceutical and pre-clinical tests and clinical trials;
- a summary of the pharmacovigilance system; and
- the risk management plan proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorization safety data.

The current medicines regulatory framework does recognize that MA applicants will not always be able to produce full dossiers of robust clinical data at the time of MA application and provides for mechanisms to address this issue, allowing authorization in a variety of special circumstances where there is sufficient justification. There are existing legal mechanisms in the EU that facilitate earlier licensing of medicines. These routes include conditional and exceptional circumstances authorizations and accelerated assessment.

Existing legal mechanisms

Conditional marketing authorizations

Conditional marketing authorizations (CMAs) were introduced under Article 14.7 of Regulation 726/2004 allowing an MA to be granted subject to certain specific obligations, to be reviewed annually by the EMA. European Commission Regulation 507/2006 and the December 2006 guideline on conditional marketing authorizations go into the detail of applying for and maintaining CMAs. Under Article 2 of Regulation 507/2006, CMAs are available for medicinal products for:
- preventing or diagnosing seriously debilitating diseases or life-threatening diseases;
- emergency situations; and
- orphan diseases.

Under Article 4 of Regulation 507/2006, a CMA may be granted where, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:
- positive risk-benefit balance;
- a likelihood that the applicant will subsequently be in a position to provide the comprehensive clinical data;
- unmet medical needs will be fulfilled – meaning that a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorized in the EU or will be of major therapeutic advantage to those affected; and
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Under Article 5 of Regulation 507/2006 specific obligations may be imposed on the holder of a CMA, eg to complete ongoing studies, or to conduct new studies.
Exceptional circumstances

Article 14.8 of Regulation 726/2004 and Article 22 of Directive 2001/83 state that in "exceptional circumstances", and following consultation with the applicant, the MA may be granted subject to certain conditions, in particular relating to the safety of the medicinal product and notification requirements to the competent authorities. The MA may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons.

Accelerated assessment

Article 14.9 of Regulation 726/2004 provides that an application may be submitted for an MA for a product which is of major interest from the point of view of public health and in particular therapeutic innovation, under which the assessment time may be reduced from 210 to 150 days.

There have been noted examples of where genuine breakthrough products, such as Vertex Pharmaceuticals’ Kalydeco (ivacaftor), has rapidly proceeded through the current regulatory system. Kalydeco is an orphan product that was granted (approved) with conditions. It is licensed for the treatment of cystic fibrosis (CF) in patients aged six years and older who have a G551D mutation in the CFTR gene. The accelerated assessment procedure was recommended by the EMA’s Committee for Medicinal Products for Human Use (CHMP) and approved by the European Commission. The procedure started on 16 November 2011, a positive opinion was issued by the CHMP on 24 May 2012 with an obligation on the applicant of a five-year observational study and final study report of an extension study evaluating long-term safety. Late last month the CHMP recommended expanding the indication for Kalydeco to also include people with cystic fibrosis (CF) ages six and older who have one of eight non-G551D gating mutations.

In total, there are currently 13 active conditional approvals in the EU and 21 licensed under exceptional circumstances.

More generally, however, these schemes may arguably be seen to be failing some patients: the emphasis on the seriousness and rareness of the disease under current approaches may be too restrictive and exclude drugs for some diseases; the interpretation of “seriously debilitating” and “need for immediate benefit” may differ amongst stakeholders (eg regulatory authority, payer/commissioner, patient and clinician); and different countries may take different views on available treatment options.

Other potential adaptive licensing tools

In addition to CMAs and the other expedited routes to market described above, adaptive licensing is intended to build on other existing regulatory processes including:

- **scientific advice, protocol assistance and HTA advice** – the EMA can, through the CHMP, give scientific advice to companies involved in developing medicines. Protocol assistance is a special form of scientific advice available for companies developing orphan medicines.
- Companies can request scientific advice or protocol assistance either during the initial development of a medicinal product before submission of a marketing authorization application or later on, during the post-authorization phase.
- The EMA also offers parallel scientific advice with HTA bodies to allow medicine developers to establish the evidence that both parties will need to determine a medicine’s benefit-risk balance and value. A pilot for parallel scientific advice was launched in July 2010. Around 25 procedures had been finalized or were ongoing as of end-2013. A draft best practice guidance for EMA-HTA parallel scientific advice was published for public consultation in May 2014.
- **compassionate use** – compassionate use is a treatment option permitting unlicensed use (rather than early licensing) that allows the use of an unauthorized medicine for a disease with no satisfactory authorized therapies or for patients who cannot enter a clinical trial, as set out in Article 83 of Regulation 726/2004. It is complementary to national legislation to allow unlicensed use of medicines under a discretion set out at Article 5 of 2001/83.
- **pharmacovigilance tools** – the pharmacovigilance legislation (Regulation 1235/2010 and Directive 2010/84 and the new good pharmacovigilance practices) provides for post-authorization safety studies thus demonstrating that risk benefit assessment is intended to be ongoing rather than stopping at MA grant. It is anticipated that these procedures could represent the main underpinning of the proposed adaptive licensing process.
- **risk management plans** – applicants must submit a risk management plan (RMP) to the EMA at the time of application for an MA. For medicines that do not have an RMP, it is likely that one will be required with any application involving a significant change to the marketing authorization. In addition, any national regulatory authority in the EU can request an RMP whenever there is a concern about a risk affecting the benefit-risk balance of the medicine.

Conclusions

As to the scientific discussion process, there are still concerns on the part of the industry as to whether the stakeholders will really be able to step out of their traditional roles and adopt the genuinely more collaborative position inherent in the successful function of the new approach. Also, some are doubtful as to the generally higher degree of scrutiny and how that would affect future review of the product especially if the adaptive licensing approach is not pursued in that particular case.

However, as of last month the EMA had received 20 submissions, and the agency recently announced that it had selected the first two medicines to enter the pilot project.

As to the relationship between the MA and HTA, whilst in the US, when the FDA approves a new drug, it is up to the marketplace (including insurers and hospitals) to decide if they will make the treatment available to patients, in the EU, an EMA approval is only the first step towards getting a new product to patients.

Any future adaptive licensing program will therefore be valueless if payment schemes are not conceived in which perhaps the lower evidentiary standards required for adaptively licensed products are reflected in the price whilst the uncertainties are resolved. It is therefore vital that applicants and regulatory and HTA agencies agree a flexible approach to the pricing and reimbursement of such products as part of the scientific discussions. Involving HTA/payer bodies in the pilot is therefore significant.

Additionally, a little over a year ago, the European Commission said it was “not convinced” that adaptive licensing was the best way forward. It has clearly relented to a degree to allow the pilot to go ahead and its full support still appears not to be forthcoming.

Finally, whilst it is implicit that adaptive licensing has to fit within the current rules, if adaptive licensing is successful it would be hoped that there should be dedicated provisions in the next revision of Directive 2001/83 and Regulation 726/2004. Arguably more importantly, it would be hoped that over time the legal bases for both MA and pricing approval would develop greater cross-linking as opposed to the twin, largely unconnected bodies of law and practice they are today.

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