

Adaptive licensing

A new approach for authorising medicines

Despite apparent reservations from the European Commission, a new concept for licensing medicines is capturing the attention of regulators around the world as a way of ensuring that marketed drugs meet real patient needs. Adaptive licensing, as it is known in the EU, could bring the data requirements of regulators and health technology assessment (HTA) bodies closer than ever before, meaning pharmaceutical companies may have greater certainty that their drug will be reimbursed.

In addition, proponents such as the European Medicines Agency's (EMA's) senior medical officer Hans-Georg Eichler believe that, by allowing for better-informed decisions on product viability earlier in the development process, adaptive licensing could potentially decrease overall development costs and provide for more sustainable return on investment.¹ But as with most promising ideas, it faces some major challenges and needs to be put to the test.

Evolution or revolution?

The basis for adaptive licensing (also called staggered approval and progressive licensing, among other names) is 'acknowledged uncertainty', which is reduced over time as additional 'real-life' data are gathered and evaluated post-authorisation. The concept builds on the existing conditional marketing authorisation (EU) and accelerated approval (US) regulatory routes, where products are licensed earlier than they would normally be on the condition that the manufacturer carries out additional post-approval studies. These pathways, however, are limited to products for patients with serious and life-threatening conditions for which there are few or no treatment options.

The vision for adaptive licensing is much broader, as it would replace the current authorisation model and would be applicable to most new products. Dr Eichler nonetheless emphasised at a recent conference hosted by The Organisation for Professionals in Regulatory Affairs (TOPRA) that it is not intended to be a one-size-fits-all solution.²

For each product, a comprehensive development and licensing plan would be agreed in advance by the sponsor, regulators and those involved in reimbursement decisions (HTA bodies/payers). Access to the new therapy would be based on a combination of data from randomised controlled trials and real-world evidence, namely observational data from sources such as electronic medical records and patient registries.

Market access to the drug would be earlier than under the traditional regulatory approach, but it might be limited to a narrower treatment-eligible population, for example. This could be an oncology drug initially available only for those with the greatest need who would be willing to accept more uncertainty. As this uncertainty diminished with additional cycles of evidence generation, the licence, as well as the labelling and any prescribing restrictions that may have also been imposed, could be adjusted accordingly.

Dr Eichler explained that in the EU adaptive licensing is more evolutionary than revolutionary: in addition to conditional marketing authorisations, the requirement for risk management plans and five-year renewals of marketing authorisations are among the precursors.

Moreover, the new EU pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) lays the groundwork for this life-cycle approach by empowering regulators to require post-authorisation safety and efficacy studies (PASS/PAES) as a condition of marketing authorisation. Dr Eichler said the legislation was very important for the future of adaptive licensing because "it gives us the legal tools to consider this new paradigm". The chair of the EMA's scientific committee (CHMP), Tomas Salmonson, suggested at the conference that the agency was ready to pilot the concept.

However, Florian Schmidt, a legal officer from the commission's Directorate General for Health and Consumers, said that the commission had doubts about the legality of adaptive licensing, adding "we aren't convinced this is the best way forward". Mr Schmidt declined to comment further when *MedNous* asked for clarification following the conference.

The situation in the EU may be hanging in the balance, but other countries are perhaps more receptive to the idea of an adaptive licensing regime. Canada is leading the way. Robyn Lim, senior science advisor at Health Canada's Office of Legislative and Regulatory Modernization, Health Products and Food Branch, told *MedNous* that the regulator first started looking into a progressive licensing model in 2006.

Health Canada no longer calls it progressive licensing but simply 'modernization' because key concepts underpinning the model, such as benefit-risk science, will be encompassed in all future drug regulation, beginning with the orphan drug framework currently being drafted, said Dr Lim.

Moreover, Health Canada has replaced the 'benefit-risk' terminology with 'benefit-harm-uncertainty (BHU) management', to more accurately reflect its approach. BHU management recognises a life-cycle paradigm that aims to enable better informed, more meaningful, more clearly communicated regulatory decisions so that other healthcare partners can make their own best decisions. It "provides direct confrontation of uncertainties in drug evidence/use that would be needed for adaptive licensing," explained Dr Lim.

In changing the paradigm, Dr Lim said, "We're not just trying to be scientifically responsible, but also socially responsible. This requires agreement among healthcare system decision-makers – including regulators, industry, payers, pharmacists, prescribers and patients – to act upon and respect each other's roles and responsibilities".

In the US, there is also a notably stronger emphasis on multi-stakeholder involvement in the drug evaluation process. A report by the President's Council of Advisors on

Science and Technology (PCAST) recommends the inclusion of patient advocacy groups and payers, among others, in the consultation process for a Food and Drug Administration (FDA) study to explore adaptive approaches to drug approval.³

On the other side of the world, Singapore's Health Sciences Authority (HSA) is also looking to pilot adaptive licensing. HSA chief executive John Lim sees the model as "an important measure to augment the current system" and envisages its use for chronic diseases in particular.⁴

Although the various countries are at different stages, they are keen to keep up the momentum. To this end, the EMA, the FDA, Health Canada, the HSA and Swissmedic, along with global pharmaceutical companies, healthcare providers, HTA bodies/payers and other stakeholders, have joined forces with the Massachusetts Institute of Technology (MIT) under a collaboration called the New Drug Development Paradigms (NEWDIGS). It seeks to provide a neutral 'safe-haven' setting for the partners to model different adaptive licensing scenarios.⁵

Alignment with payers

To achieve the full potential of adaptive licensing, a 'systems approach' whereby licensing decisions are ideally aligned with coverage and prescribers' decisions is necessary, according to Dr Eichler. HTA bodies had an opportunity to share their perspectives during the TOPRA conference.

Carole Longson, director of the UK National Institute for Health and Clinical Excellence (NICE) Centre for Health Technology Evaluation, welcomed the adaptive licensing concept, noting that it was quite compelling to see regulators thinking "like HTA bodies think".

Nevertheless, she cautioned that "real life is very complex and regulators have to accept that it's not just regulatory aspects that'll need to be considered in adaptive licensing... Adaptive licensing aligns very well with the way HTA bodies think but we've got to get it right". This means developing a system that does not increase uncertainty and "keeping in mind that risks are being moved, not removed".

Thomas Müller, head of the Pharmaceuticals Department at Germany's Federal Joint Committee (G-BA) warned that adaptive licensing "could erode trust" and suggested there could be a potential conflict of interest if regulators showed interest in getting a product onto the market. He added: "The crisis of drug development – spoken about a lot in the context of adaptive licensing – should not be directly linked to licensing concepts."

Indeed, Finn Børllum Kristensen, secretariat director of the EU network for HTA (EUnetHTA), believes that it is of fundamental importance to keep the two decision streams (ie regulatory and reimbursement) clear of each other. "Not that they are not overlapping or that there should not be a lot of exchange of information and collaboration – but they are different," he told *MedNous*.

Despite this caveat, Dr Kristensen said that adaptive licensing could be a step forward in terms of bridging the gap between regulatory and HTA data needs. "It's about the same need for follow-up or for substantiating uncertainty associated with licensing... But for HTAs the agenda would be broader than that of regulators."

Challenges remain

Advocates of adaptive licensing are well aware of the potential public perception that regulators would be lowering standards for allowing drugs onto the market. Therefore, any such system would have to include communication to stakeholders that the aim is actually to get more robust and relevant data earlier, and throughout product development.

Stakeholders would also have to be educated and accept that initial approval is conditional upon further studies. But will industry agree to carry out so-called post-initial authorisation studies? Even if manufacturers were willing to do these studies, whether or not they are feasible or even ethical remains to be seen. Dr Müller pointed out, for example, that there is no legal framework in Germany to guide drugs with adaptive licences into further research.

In addition, Dr Salmonson brought up the issue of 'equipoise', or genuine uncertainty, which is a key ethical principle of randomised controlled trials. Where there is equipoise, no participant in a trial is knowingly given an inferior treatment. But once a new drug has been assessed by regulators, it could be argued that equipoise has been lost and thus the trial could be considered unethical.

Another issue is whether industry will accept the impact of adaptive licensing on patents and exclusivity periods, as the clock would start ticking under the initial, more restricted authorisation.

Furthermore, healthcare professionals would need to be on board. Health Canada's Dr Lim pointed out that this would be beneficial because, for example, "uncontrolled off-label use, with no ability to feed information back into the system to allow for continuous learning, is not the way we would want to go."

And finally, the age-old question remains: Will the drug be reimbursed?

References

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