ABPI briefing

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Adaptive licensing

Adaptive (or progressive) licensing of new medicines is an alternative approach to the current established system of marketing authorisation. Adaptive licensing means 'drug candidates' that meet a serious unmet medical need can be initially approved for use in a restricted patient group, with their use then gradually expanded to broader patient populations as additional safety and efficacy data is generated. This allows licensing to align more closely with patient needs for timely access to new medicines, and for data to be gathered on an ongoing basis. Adaptive licensing is a part of adaptive trial design, which is increasingly being introduced and accepted within the current authorisation procedures. There are already some provisions in the current regulatory regime which add a level of flexibility to the licensing process, hence the adaptive approach involves formalising what has previously been done ad hoc.

Key features of adaptive licensing

- An initial authorisation based on early risk/benefit assessment in an agreed restricted population, with strong efficacy signals. This is followed by iterations of prompt label adaptations informed by data from monitoring of 'real world' efficacy and safety. These post-initial approval commitments should be made clear from the outset and their feasibility agreed upfront.
- All stakeholders contribute to a prospective development plan and input into the design of the confirmatory trials.
- Customised drug and disease specific licensing pathways are set up that may utilise existing regulatory mechanisms.
- Managed market entry controlling patient access with reimbursement being linked to continued data collection, which informs value assessment.
- Working within existing provisions for flexibility in the current regulatory regime.

Benefits of adaptive licensing

The benefits of adaptive licensing are clear:

- It meets the needs of patients through enabling earlier access to medicines.
- It increases the efficiency of the drug development process.
- It helps to bridge the 'valley of death' [1] funding gap for Small to Medium Sized Enterprises (SMEs).
- It can provide better evidence of value and potential for cost savings in the healthcare system.

1. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf

Challenges of adaptive licensing

In order for adaptive licensing to be successful, a number of challenges must be overcome and questions answered, including:

- Inclusion criteria - the medicine must be a substantial advance for patients in areas of serious unmet need, but how is this established?
- Risk management - how to involve and secure agreement from stakeholders such as patients, doctors, NHS and industry in these activities? Eg. adaptive licensing relies on strict prescribing practice particularly in the initial licence period.
- Methodology - could novel trial designs facilitate the adaptive licensing?
- How will these medicines be reimbursed particularly when initially authorised? Under what circumstances would the price be revised, and on what grounds?
- Confirmatory data - what is collected, over what period, and who funds this?
- How to sequence initial versus subsequent indications?
- If benefits are not confirmed in certain populations, how would withdrawal work?
- Data exclusivity - launching a drug first in a small restricted population may affect the ability of the drug developer to recover a return on investment into R&D as data exclusivity will begin counting down earlier, once initially authorised, but without full reimbursement.
- Regulators must be willing to accept data that could contribute validly to assess benefit/risk before licensing, backed up with enhanced post-marketing safety and efficacy surveillance to manage uncertainty.

The current landscape

Adaptive licensing builds on existing regulatory processes and intends to extend the use of elements that are already in place, including:

- Scientific advice
- Centralised compassionate use
- The conditional marketing authorisation mechanism (for medicines addressing life-threatening conditions)
- Patient's registries
- Pharmacovigilance tools that allow collection of real-life data and development of risk management plans

A number of proposals have been adopted over the last few years in the EU and UK in an attempt to achieve a more progressive and adaptive approach to licensing. The Medicines and Healthcare products Regulatory Agency (MHRA) recently launched Early Access to Medicines Scheme (EAMS). [2]

European Medicines Agency (EMA) pilot

The European Medicines Agency (EMA) has recently launched a pilot project for adaptive licensing with a view to improving timely access for patients to new medicines with the assent of the European Commission. The EMA pilot will explore the adaptive licensing approach with real medicines in development, and the EMA is inviting companies to participate by submitting programmes for consideration.

Adaptive licensing requires a holistic approach with the involvement of all stakeholders who have a role in determining patient access. All discussions will take place in a 'safe harbour' environment to allow free exploration of the strengths and weaknesses of all options for development, assessment, licensing, reimbursement, monitoring, and utilisation pathways in a confidential manner and without commitment from either side. The EMA's approach seeks to maximise the positive impact of new medicines on public health by balancing timely access for patients with the need to provide adequate evolving information on their benefits and risks.

As the project progresses, the European Commission will examine the legal and policy aspects related to adaptive licensing in collaboration with the EU member states and by consultation with relevant stakeholders.

Background to the EMA's activities on adaptive licensing, the framework document to guide discussions of individual pilot studies and application forms are available on the EMA website. [3,4]

2. http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm
3. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce
4. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/03/news_detail_002046.jsp&mid=WC0b01ac058004d5c1

Progress to date

There is a range of ongoing key initiatives in major regions such as the UK, the EU and the USA. A common theme that runs throughout is the need to pilot the adaptive licensing approach to prove the concept and determine what policy change (if any) is necessary going forward.

The ABPI has long called for a more flexible licensing approach. This is in line with the view of the MHRA Innovation in the Regulation of Medicines Expert Group, that the ABPI was a member of, which called for "*adaptive licensing at the earliest opportunity so that companies could put forward pilot products*" in a report published September 2013.[5]

Due to the centralised approach, adaptive licensing will be implemented at least at EU level by the EMA, and the ABPI calls for the MHRA to play a leading role in the pilot process. There is substantial potential for the UK to be the location of choice for adaptive licensing pilots due to our favourable policy environment, such as the NHS as the main healthcare provider, powerful initiatives on electronic health records on which successful adaptive licensing will rely, and the progressive nature of its government and medicines regulator. Maintaining patient safety is of paramount importance - as evidenced by the recent announcement of a UK Early Access to Medicines Scheme (EAMS). [6] Further clarity on how the EAMS will link to adaptive licensing approaches at EU level will need to be explored. To help facilitate discussions, explore opportunities and publicise EAMS, the ABPI and the BIA jointly held a stakeholder event in May 2014. A report [7] of the meeting capturing regulatory, clinical, patient and industry perspectives is now available from the ABPI. The MHRA has recently published a leaflet [8] on how it supports innovation, including the UK Early Access to Medicines Scheme and the EMA's adaptive licensing pilot.

Conclusion

It is important that industry continues to play its part in the modernisation of the licensing process for medicines. The ABPI and its members, via EFPIA, are actively involved in UK and global level activities.

There is a clear need to increase the flexibility of medicine licensing to improve the efficiency of the drug development process and get the next generation of medicines to patients faster, whilst at all times preserving and enhancing patient safety. What is even more important is the realisation that scientific change occurs continuously and a progressive approach is needed from regulators, while maintaining patient safety, which allows faster, progressive adaptation of procedures coupled with a cultural change from both regulators and industry.

The ABPI expects adaptive licensing to help support the development of medicines where there is a high unmet need, such as novel antibiotics and medicines for dementias and rare diseases, and this pilot is a big step change. Adaptive licensing could be a significant tool in the armamentarium to support more efficient medicine development and licensing, and ultimately ensure faster patient access to innovative medicines.

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5. http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con336728.pdf
6. http://www.mhra.gov.uk/Howweregulate/Innovation/EarlieraccesstomedicinesschemeEAMS/index.htm
7. http://www.abpi.org.uk/our-work/library/industry/Pages/210514.aspx
8. http://www.mhra.gov.uk/home/groups/dts-bs/documents/publication/con413551.pdf