

Adaptive licensing — A way forward in the approval process of new therapeutic agents in Europe

Giuseppe M.C. Rosano^{a,*}, Stefan D. Anker^b, Walter Marrocco^c, Andrew J.S. Coats^d

^a Cardiovascular and Cell Science Institute, St. George's University of London, London, UK

^b Chair of Innovative Clinical Trials, University of Gottingen, Germany

^c F.I.M.M.G. — Federazione Italiana Medici di Famiglia, Rome, Italy

^d Monash–Warwick University Alliance

Available online 4 February 2015

Modern medicine is moving towards more specific individualised therapies that can target diseases in individuals with specific characteristics. For each disease it is now possible to genotype and divide patients into different groups that will respond differently to the same treatment aimed at treating the overall disease. This will lead at a more effective therapeutic approach that will maximise the benefit of a given treatment and will limit the potential occurrence of serious adverse events.

The need for tailored therapies will necessarily transform the knowledge cycle of therapeutic innovation that goes from cutting-edge discovery through comprehensive development and regulation to clinical application and utilisation. The regulatory bodies have adapted their regulations to the changing scenario issuing different regulations for granting marketing authorisation to drugs aimed at specific patient populations or conditions [1]. The European Medicine Agency has been the most innovative Agency in the field issuing regulations such as the conditional marketing authorisation, the marketing authorisation under exceptional circumstances (Directive 2001/83EC) and post-authorisation efficacy studies (PAES) [1,2]. These regulations together with the new pharmacovigilance legislation and the implementation of the risk management plans, periodic safety update reports (PSURS) and the legislation on the five year renewal of marketing authorisation have all been the precursors of the newly launched programme of adaptive licensing [3].

The project has been launched in March 2014 by the European Medicine Agency and represents an extremely innovative method to grant marketing authorisation for drugs aimed at disease where

there is an unmet medical need [4,5]. The adaptive licensing is a prospectively planned, adaptive approach to bring more rapidly a promising new medicinal product for an unmet medical need to the market. The programme starts with an authorised indication in a “niche” indication followed by iterative phases of evidence gathering coupled with licensing adaptations. These will involve the authorised indication but may also include the potential expansion to further therapeutic uses of the medicinal product. The adaptive licensing process tries to guarantee the positive impact of new drugs on public health for conditions with an unmet medical need by balancing a rapid access for patients with the need to gather adequate information on benefits and harms. The promoter (sponsor) must show evidence to support a positive benefit–risk in a defined sub-population at the time of initial licensing. This may include benefit on surrogate pharmacodynamic endpoints. Furthermore, the sponsor must give assurance of commitment to conduct further studies after the initial marketing authorisation.

The adaptive licensing changes the usual way of thinking at drug development and at the time-course of evidence gathering with a new therapeutic agent before reaching marketing authorisation. Under the current regulations before applying for marketing authorisation almost all patients treated with the therapeutic agent are included in randomised controlled trials to demonstrate efficacy and open label studies to explore safety or to other types of interventional studies. However, when the marketing authorisation is granted, the treated exposed population expands rapidly without contributing significantly to generation of evidence on efficacy or on safety.

With the adaptive licensing pathway the number of patients included in pre-approval randomised control trials may be smaller and the initial marketing authorisation may be granted with more limited evidence as for the current regulation but

* Corresponding author at: Cardiovascular and Cell Science Institute, St George's University of London, Cranmer Terrace, London SW17 0RE, UK.

E-mail address: giuseppe.rosano@gmail.com (G.M.C. Rosano).

with a commitment by the marketing authorisation holder of further confirmatory studies to be conducted to confirm the efficacy in the approved indication and to expand into other indications. Once approved, the medicinal product will be distributed under a monitored environment possibly through appropriate registries validated by regulatory bodies. Therefore, under the adaptive licensing framework the number of patients that will be treated with the therapeutic agent will grow slowly because of the prescribing limitations. All patients exposed to the new therapeutic agent will either be included in new randomised clinical trials or captured by some form of observational study/registry, thereby contributing to real-world (effectiveness) information. A full license may be granted only after the delivery of the pre-agreed milestones and the active surveillance measures will be gradually eased.

It is important to clarify that the adaptive licensing pathway implements the regulatory processes within the existing EU legal framework. These include scientific advice, compassionate use, conditional marketing authorisation, marketing authorisation under exceptional circumstances, pharmacovigilance legislation including risk management plans and use of patient registries. One important feature of the adaptive licensing pathway is the involvement of the HTA bodies and/or payers together with stakeholders in the process.

The aim of adaptive licensing is to guarantee a timely availability of promising new treatments that address conditions where there is an unmet medical need. This can be defined by a therapeutic area where no satisfactory alternative therapies exist or where the existing therapies are not adequate to curb the mortality and morbidity of the disease.

The European Medicine Agency has given ample assurance that the interactions between stakeholders will take place in a safe harbour environment in order to explore all options

for development, licensing and assessment. After the initial engagement more formal interactions such as scientific advice or protocol assistance will be needed. Therapeutic agents to be considered for the adaptive license pathway will be experimental drugs or biologicals in the early stage of clinical development prior to initiation of confirmatory studies.

In conclusion, the new adaptive licensing pathway paves the way to a more rapid access to market for drugs to be tested and put in the market under controlled conditions. The earlier market access will have to be balanced by a progressive adaptation of prices of the therapeutic agent approved through the adaptive licensing given that the agent will benefit from a longer patent protection being early on the market.

References

- [1] Committee For Medicinal Products For Human Use (CHMP). Guideline on procedure for the granting of a marketing authorisation under exceptional circumstances, pursuant to article 14 (8) of regulation (EC) No 726/2004. London 15 December 2005. EMEA/357981/2005 http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004883.pdf.
- [2] European Medicines Agency. Post-authorisation safety studies (PASS) and post-authorisation efficacy studies. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000377.jsp&mid=WC0b01ac058066e979.
- [3] European Medicines Agency. Plan for implementation of the pharmacovigilance legislation by the European Medicines Agency. 2 February 2012 EMA/64750/2012 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500121837.pdf.
- [4] European Medicines Agency. Pilot project on adaptive licensing. 19 March 2014 EMA/254350/2012 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/03/WC500163409.pdf.
- [5] Eichler HG. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther* 2012;91(3):426–37.