The evolution of European Medicines Agency drug approval: the adaptive licensing

C Di Giorgio,[1] S Adami,[2] A Provenzani,[1] S Bianchi,[3] N D'Alessandro,[4] P Polidori[1]

In March 2014, the European Medicines Agency (EMA) launched a pilot project of 'adaptive licensing' to speed up access to drugs in development, in order to respond to unmet medical needs. The project will involve parallel scientific advice from the regulatory agency, pharmaceutical industry, the companies Health Technology Assessment (HTAs) bodies, organisations studying guidelines on clinical treatment and patient associations.

The traditional process of drug authorisation is divided into several parts, involving in vitro studies and in vivo studies in animals (preclinical studies), as well as phase 1–3 randomised controlled trials conducted in humans over a predefined period. When authorisation is granted, the drug is intended for a larger population. Some patients, depending on the type of drug, may be entered into register studies and/or followed by other forms of pharmacovigilance studies.[1 2]

According to the adaptive licensing process, however, initial drug authorisation may be granted on the basis of clinical studies involving a limited number of patients and thus is faster than the normal process. After the initial granting of the license, the number of patients treated slowly increases. The latter are enrolled in various forms of observational studies so as to generate information on the effectiveness and adverse effects of the drug in the real world. Only after these different and programmed steps can a drug be granted a 'full license'.[1 2]

The adaptive licensing project launched by the EMA has many strengths, such as early access to certain medications for the treatment of particularly serious diseases where there are no therapeutic alternatives, producing almost immediate information about the drug's effectiveness in the real world and the production of a useful advance for pharmaceutical companies. Within such a delicate process in which patient safety is central, can these strengths really be considered advantageous? On the one hand they represent very important opportunities, but on the other hand there are real weaknesses. Advanced authorisation is closely linked to a greater degree of uncertainty of the risk/benefit profile of the drug. According to the EMA, the feasibility of the adaptive licensing depends on the willingness of all parties involved in the process, including patients, to accept a higher level of uncertainty of the product authorised. How much uncertainty is permissible? Moreover, is it right to involve patients in the choice of the uncertainty degree as they are emotionally and physically involved while at the same time not having specific knowledge to make a rational and objective assessment? With accelerated approval, fewer patients are enrolled to demonstrate a benefit in a short time. The proven benefit inevitably will be based on endpoints evaluated in a limited number of patients in a reduced exposure time. This will not allow us to evaluate the effects of long term and major events related to the new treatment (ie, prolonged survival, reduction in mortality or incidence of a disease, etc).

An accelerated license does not allow for evaluation of the toxic effects of a long term therapy, and the data derived from a small sample of patients will never have the same significance as those gained from studies in a larger population.

In addition, pharmaceutical companies that have a product approved with this procedure will generate profits immediately, so will they have the same interest in conducting clinical trials with valid endpoints which are strongly dependent on the sample size and duration of the study in order to demonstrate the effectiveness or otherwise of a new product? Normally, a pharmaceutical company invests significant resources to recruit hundreds or maybe thousands of patients to be followed over long periods. The costs of research, therefore, depend also on the size of the sample and the time employed for the study. With this new procedure, the company would significantly reduce research costs and still get the profits from an immediate commercialisation of a medicine (table 1).

The question of the cost of research, and the price of the drug authorised under the procedure of license adaptive and reimbursement have not yet been clarified. According to the EMA, it would need to agree in advance the price and terms of repayment of the new drug for different levels of authorisation—that is, after the initial license, after any subsequent license and after the final one.[1 2]

Yet, how will the process of adaptive licensing fit with regulatory procedures that allow the off-label use of drugs (eg, law 648/96) or access to experimental therapies (eg, DM 8/5/2003)?

There is already a procedure for the EMA to grant a license with conditional approval before all of the data are

Table 1 Advantages and disadvantages of the adaptive licensing

Advantages of adaptive licensing	Disadvantages of adaptive licensing
Anticipated access to medicines for the treatment of serious diseases with no therapeutic alternatives	Greater degree of uncertainty of the risk/benefit profile of the drug
Immediate information on the effectiveness of the drug in real life	No assessment of the toxic effects of long term therapy
Rapid production of profits for pharmaceutical companies with reduction of the costs of clinical trials	Lack of significance of the results obtained from studies conducted on a restricted population
	Little interest of pharmaceutical companies to conduct post-marketing studies for an approved drug and which provides profits
	Need to define the modalities of implementation of the adaptive licensing project

[1]Department of Clinical Pharmacy, Mediterranean Institute for Transplantation and Advanced Specialised Therapies (ISMETT), Palermo, Italy; [2]Pharmaceutical Service Veneto Region, Verona, Italy; [3]Hospital Pharmacy Department, University Hospital Ferrara, Ferrara, Italy; [4]Department of Health Promotion Sciences, Section of Pharmacology, University of Palermo, Palermo, Italy

Correspondence to C Di Giorgio, Department of Clinical Pharmacy, Mediterranean Institute for Transplantation and Advanced Specialised Therapies (ISMETT), Palermo 90127, Italy; digiorgio82@hotmail.it

available. However, this procedure is valid for only 1 year, during which time ongoing studies must be completed to provide clinical data and meet the other requirements imposed at the time of authorisation. Also, periodic reports must be submitted on request or at least every 6 months. The conditional license is issued if the benefits outweigh the potential risks associated with the lack of additional data.

The adaptive licensing project is attractive for many reasons. A drug, although characterised by a high level of security, if made available too late, is not useful for the patient.[3] Thus to identify therapy promptly means ensuring patients a greater opportunity of remission or cure of the disease. However, access to this procedure should be limited to cases of real and unique needs, where no adequate treatment options are clearly identified.

Many points remain to be clarified with regard to this innovative process. It is important to understand if and how monitoring tools (eg, L'Agenzia Italiana del Farmaco (AIFA) monitoring lists) will be activated to promote and ensure the appropriateness of innovative and high cost drugs, collect post-marketing data to evaluate effectiveness in real life situations and govern reimbursement mechanisms by national health services according to specific final results.

The desirable goal of all clinicians involved in the drug authorisation process should be to ensure effective and safe therapies whose benefits persist over time and for an ever increasing population. It is also important to ensure that the required timeliness for the authorisation is not going to compromise the quality of the final product.

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REFERENCES

1 Eichler HG, Oye K, Baird LG, *et al*. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther* 2012;91:426–37.
2 Bozzini L, Font M. Un progetto dell'EMA: licenza adattiva dei medicinali. Piano di accesso progressivo dei pazienti alle cure. http://www.ulss20.verona.it/data/29/Informazioni/InfoFarma_5_2014.pdf
3 AIFA. Verso percorsi adattivi di valutazione dei farmaci: il punto di vista di AIFA ed EMA (online). Consulted 2015, June 25. http://www.agenziafarmaco.gov.it/it/content/verso-percorsi-adattivi-di-valutazione-dei-farmaci-il-punto-di-vista-di-aifa-ed-ema