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EXPERT OPINION



# Innovative medicines: new regulatory procedures for the third millennium

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Despite tremendous progress in science and increasing investment in research and development, patients' access to innovative medicines remains limited. This is in part due to increasing regulatory requirements for product authorisation and cost-constrained national health systems. At the European Medicines Agency (EMA), we have tried to address these constraints by adapting our organisation and activities to changing business models, new technologies, and the current and emerging health needs in Europe. The main EMA initiatives to provide patients with effective, safe and affordable medicines are reviewed.

**Keywords:** adaptive licensing, clinical trials, European Medicines Agency, health technology assessment, innovative medicines, transparency

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## 1. Introduction

Despite tremendous progress in science and increasing investment in research and development (R&D) by the pharmaceutical industry, the rate of introduction of innovative medicines has remained roughly stable over recent years [1]. Furthermore, the number of clinical trials has generally declined in Western countries, as have the revenues from R&D, despite a recent apparent inverted trend and some exceptions poorly predicted by analysts [2]. As a result, and at a time of increasing globalisation, investors have been diverted to more promising markets outside of Europe and the United States of America.

Although discovery of innovative drugs mainly reflects the capacity of industry, therapeutic innovation itself is the result of a more complex system, involving politicians, scientists, investors, regulators and payers. It is clear that the ability of industry to innovate is influenced by laws, cost-constrained health systems and increasing regulatory requirements for product authorisation.

We, at the European Medicines Agency (EMA) have been reflecting carefully on the potential constraints on innovation in medicines. We have tried to counteract these constraints by adapting our organisation and activities to changing business models, new technologies, and to the current and emerging health needs in Europe.

## 2. EMA initiatives for innovation

Several initiatives have been implemented at EMA to provide support for pharmaceutical innovation from the very early stages of development and during the entire cycle of drug evaluation. These initiatives aim to provide citizens with new safe and effective medicines while reducing the uncertainty surrounding a risky commitment for industry and investors.

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### 2.1 Enhancing dialogue with all stakeholders

A closer communication among all drug stakeholders has been recommended by the WHO Report on Priority Medicines for Europe and the World [3]. We hope to achieve this at EMA through a number of initiatives, including the early involvement of patient associations in the drug evaluation process and by the creation of the Health Care Professional Working Parties, aimed at facilitating a bilateral communication with health-care providers and scientific societies operating in different areas of medicine.

A close collaboration between academia and regulators is also seen as particularly desirable. Persisting distrust from both sides should be overcome in order to share experience and to collaborate on joint projects for independent research, education and personnel, possibly with the financial support of Horizon 2020 and the IMI2 programmes.

The business pipeline activity was set up by EMA to establish a confidential and mutually beneficial discussion with pharmaceutical companies to discuss their products' regulatory pipeline, including marketing-authorisation applications and paediatric investigation plans. It aims to identify issues impacting the drug portfolio of companies, anticipate their operational needs to ensure high standards for submissions of dossiers, and to identify the most appropriate resources, scientific expertise and guidelines for them at an early stage.

The business pipeline and the pre-scientific advice meetings may be particularly useful for small and medium enterprises (SME), which often do not have the background, facilities and financial resources available for big Pharma. EMA has devoted an *ad hoc* office to SME as a result of the observation that over 50% of innovative medicines come from academia and SME [4].

Scientific advice is a tool to help developers decide the best study design including selecting optimal population sample and outcome measures when developing a new drug. A joint scientific advice with EMA and FDA will avoid marked differences in the studies included in dossiers presented to both regulatory bodies.

### 2.2 Qualification process

There is no doubt that the time of blockbuster drugs has come to an end. This does not mean that there will be no drugs providing revenues of more than one billion dollars in the future, but that the 'one size fits all' concept is no longer accepted either by patients or by national health services. Patients now expect bespoke drugs that are effective and safe for them and not for a virtual 'average' patient with the same disease, whereas financially stretched national health services are only prepared to pay the increasing costs of new drugs for selected populations of responders. It is therefore time to move to a precision medicine model, supported by evidence-based criteria and validated biomarkers that allow disease phenotyping and a new nosography of diseases [3].

The qualification process is a new, voluntary scientific pathway leading to a qualification for innovative methods, biomarkers and drug-development tools. Sponsors are encouraged to apply for qualification advice at an early stage and before initiating studies in order to receive EMA feedback on the design of the studies and the overall strategy. Alternatively, if data are already available to support claims, a qualification opinion is a more suitable procedure [4].

### 2.3 New methods for the evaluation of medicines

The number of applications for biologicals is increasing, with a trend that will soon see biologicals overtake chemical products, which have been declining over recent years. The number of patents expiring for biologics will also increase in the next few years, resulting in a greater number of applications for marketing authorisations for biosimilars. The number of gene therapies is increasing too.

Gene therapies, advanced cell therapies, biological and biosimilars cannot be adequately evaluated by the methods used in the past for chemical drugs.

Glybera (alipogene tiparvovec), the first gene therapy to be approved in the Western world in 2012, represents an example of the problems encountered in the evaluation of this new generation of medicines. The drug was approved for the treatment of a clinically heterogeneous condition with a risk of life-threatening pancreatitis on the basis of data from 27 patients only with results referring to a primary end point different from that originally set, and following some divergent opinions of different EMA bodies [5].

Similarly, classical case–control statistics cannot be readily applied to rare diseases, which affect a very small number of patients. Inclusion of a control group in studies in these diseases is often impossible. This calls for new study designs and modelling, as well as for new approaches in the evaluation of medicines.

### 2.4 New licensing pathways

At present, in all types of marketing authorisation (normal, conditional, exceptional) approval is a binary decision at a given moment of the development of a medicine. With adaptive pathway, EMA is starting to explore a new marketing-authorisation pathway to facilitate patient access to medicines [6]. Adaptive pathway replaces the traditional binary approval/non-approval decision with iterative phases of evaluation of a drug through evidence gathered during its entire life cycle. It also takes advantage of elements introduced after its first approval, by the new pharmacovigilance legislation, post-authorisation efficacy and safety – including real-life – studies, and *ad hoc* registries. A call for pilot studies on this facilitated pathway for a timely access to drugs has been made by EMA recently.

### 2.5 Facilitating access to medicines for the patients

The process for successfully bringing a new medicine to marketing authorisation is a risky, slow and difficult challenge.

It is estimated that only 1/5000 – 1/10000 molecules will be successful. Even when marketing authorisation is obtained, health technology assessment (HTA) and decisions on drug pricing and reimbursement often delay access to medicines for patients at national (or even regional) level. This is likely to worsen in the future, because of the increasing costs of drugs, particularly of biologics.

This was the case for instance for Ivacaftor. Ivacaftor (Kalydeco®) modifies the impairment of the cystic fibrosis transmembrane conductance regulator caused by the mutation G551D in its gene (where glycine in position 551 is replaced by aspartic acid). This mutation is present in 4 – 5% of cystic fibrosis patients and causes a block in chloride ion access into epithelial cells, which turns into the sticky mucus typical of the disease. Ivacaftor was designated as an orphan drug and showed a marked effect on FEV1 compared to placebo. It therefore obtained marketing authorisation by both FDA and EMA in 2012, after only 4 years from presentation of the dossier to EMA. Unfortunately, due to its high cost, in 2014 the drug was only available for patients in < 50% of European countries and it is still undergoing HTA in most countries.

An early dialogue between regulators and HTA bodies, without limiting the autonomy of local authorities to take decisions about reimbursement policies, may help in evaluating whether the risk–benefit of a new drug is associated with the efficient use of resources at an early stage. At present, 35 procedures of joint scientific advice between EMA and HTA bodies have been activated in different areas of medicines.

This new approach might help identify key outcome measures for decisions of HTA national bodies at a very early stage of drug development.

### 2.6 Adapting technology infrastructures to new needs

The large amount of data emerging from the new Clinical Trial [7] and Pharmacovigilance [8] legislations as well as from the recent EMA transparency policy on the pro-active publication of clinical trials data [9,10] represents a relevant challenge that EMA is facing by enhancing information technology infrastructures for gathering, validating, processing and analysing all the information made available.

## 3. Expert opinion

Progress in science in order to have a translational impact on access of patients to innovative medicines cannot only rely on increasing investment in pharmacological R&Ds. The new regulatory procedures briefly reviewed represent the efforts of the EMA to overcome some potential regulatory constraints on innovation in medicine. However, innovative drugs may only result from a new 'innovation system' based on a joint collaboration and an effective communication among all stakeholders, including investors, academia, industry, politicians, regulators and payers.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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