The technological advances built upon progressive understanding of the human genome and cell biology have led to a growing number of new therapies. In the past five years, about a third of applications for marketing authorization received by the European Medicines Agency (EMA), were for biotech medicines, including recombinant DNA, fusion proteins, and monoclonal antibodies. Gene therapies are emerging and have proven effective in treatment of severe combined immunodeficiency and show promise in treatment of hemophilia B.

Despite the scientific progress, developing medicines to treat rare diseases represents a particular challenge, as their low prevalence—no more than 5 in 10,000 people in the European Union (EU)—contributes to an uncertainty with regard to the return on investment. In 2000, the Orphan Medicinal Product Regulation was introduced in the EU, with the purpose of stimulating therapeutic innovation in rare diseases, allowing marketing authorization applicants to receive clinical trial protocol assistance, fee waivers for the regulatory procedures, and a 10-year market exclusivity.

To date, 126 orphan medicines have received EMA approval. However, the unmet medical need is still high. For the more than 7,000 known orphan diseases affecting between 30 and 40 million people in the EU, only about one percent are currently addressed with an adequate treatment. With an annual cost of 150,000 euros ($167,000) per patient on average and about 1,620 orphan medicines estimated to be in development, decisions on the allocation of intrinsically limited national budgets across existing and emerging therapies are becoming increasingly difficult. The Healthcare Ministries (further referred to as ‘Payers’) have been ringing alarm bells on the high prices of medicines and there is a growing concern about the sustainability of healthcare systems in Europe.

A typical response by Payers to an increasing number of expensive medicinal products has been price cuts, compulsory rebates, and increased patient co-payments. Whether this approach can ensure patient access and stimulate biomedical research in the long term is questionable. It has been acknowledged that, if left unchanged, this approach may lead
NEW APPROACHES TO EVIDENCE GENERATION

In order to understand whether health technologies are worth their price, the costs associated with their use have to be weighed against the respective health gains. Traditionally, the efficacy of a drug has been analyzed by means of frequentist statistics, i.e. a comparison of between-group difference of statistical means observed within a randomized controlled trial (RCT), powered based on an ‘a priory’ assumed effect. A consensus has been growing, however, that this approach may neglect the variability in patient response resulting from the biological complexity and variation of the human phenotype. Particularly in rare diseases, where adequate enrollment numbers are often unfeasible, and the mechanism of action of a drug not entirely understood, compulsory RCTs may slow the scientific progress. The need for a methodological shift to adaptive trial designs, which allow for iterative evidence generation and a timely recognition of the drug efficacy in certain subgroups has been recognized. Innovative regulatory concepts have been put forward by EMA, such as adaptive pathways and conditional marketing authorization, with mandatory post-licensing data collection accompanied by an appropriate risk management plan. The purpose of these currently piloted methods is to facilitate quicker patient access to new therapies addressing high medical need while reducing time and costs associated with large clinical trials. To ensure such post-authorization real-life evidence generation development and routine use of uniformly designed European patient registries seems essential.

EUROPEAN COOPERATION ON HEALTH TECHNOLOGY ASSESSMENT

A European marketing authorization does not guarantee reimbursement at the national level. Twenty-seven national decisions on the therapeutic added value and price of each drug need to be taken within the EU. A scientific assessment of the added therapeutic value of new medicines compared to the best available alternative and in relation to the associated costs is the purpose of Health Technology Assessments (HTAs).

So far, HTAs have only been partially successful in increasing the transparency of the reimbursement decisions. Due to many methodological differences of the national HTAs, a concordance on the therapeutic value of medicines in the EU seems to exist for no more than 50 percent of the new drugs. These differences in scientific judgment are difficult to explain to patients who are evolving toward an assertive, well-informed stakeholder within the healthcare sector and wonder why access to often life-saving treatments is not equal across the EU countries. Differences in the countries’ purchasing power represents an additional challenge. The rapid expansion of the EU, following the post-Soviet application of the East European countries, has been one of the EU’s most successful foreign policies, but has created economic inequalities within the EU. The cross-border-care directive (2011/24/EU) that assumes similarity of the healthcare provision, promotes work toward reducing the gap in healthcare quality within Europe.

In past years, these issues have been addressed through different initiatives at the scientific and policy levels. The European Commission has put considerable effort into the “European Network for Health Technology Assessment” (EUnetHTA) project, a voluntary network of the national HTA
bodies, aimed at joint assessment of health technologies, with the purpose of avoiding duplication and increasing transparency and outcome consensus of the scientific work, particularly with regard to the relative clinical benefit of new treatments. After developing common methodologies and piloting joint HTAs during the previous Joint Actions (2010–2015), the newly begun “Joint Action 3” of EUnetHTA aims to increase the number of joint assessments and establish a permanent mechanism for European cooperation on HTAs by 2020.

Since 2010, the EMA and EUnetHTA have cooperated on several topics related to the evaluation of medicines, e.g., design of adaptive pathways and an early alignment of the evidentiary requirements between the regulatory and HTA bodies through parallel scientific advice. Such cooperation has potential to facilitate efficient and adequate data collection to support the companies’ reimbursement requests and accelerate patient access to effective treatments. Further success of the European HTA cooperation will be measured by the extent to which different Member States will be willing to integrate the results of joint assessments into their reimbursement decisions. In the meantime, BeNeLux (a union of Belgium, the Netherlands, and Luxembourg), joined by Austria, is pioneering a proprietary cooperation on joint horizon scanning, HTAs, and principles of price negotiations on orphan drugs. Ten Eastern European countries with lower but comparable gross domestic product levels, have announced plans for similar cooperation. The role of the EC as a coordinating party has yet to be clarified and fits in the general debate on the purpose and scope of the joint activities within the EU, notably provoked by the recent decision by the United Kingdom to leave the EU (Brexit).

Citizen engagement in the reimbursement decisions

Citizens’ role in the reimbursement decisions is still very limited, due to a historically paternalistic functioning of the healthcare systems on one hand, and a specialized nature of such decisions on the other. Difficult ethical choices are often being made by the Payers without sufficient insights into the societal “willingness to pay”. In order to justify the reimbursement decisions within the publicly financed European healthcare systems, citizen engagement in policy-making seems crucial. Methods to structurally elicit the population’s views on reimbursement priorities are under exploration and may support decisions on the affordability of therapies to treat rare diseases.8, 9

As discussed above, the primary concern of the policy-makers at the moment seems to be the budgetary impact of new therapies. Among the emerging ‘managed entry schemes’ for expensive medicines, for instance, the price-volume contracts clearly outnumber the pay-for-performance agreements. Linking prices of medicines to their value would create a rational benchmark for budget allocation and increase transparency in the reimbursement decisions. Further conceptualization of ‘value’ will require more active patient involvement in the development and evaluation of health technologies and will enhance our understanding of the outcomes that are truly relevant.10

References: