THE EUROPEAN FILES

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Medicines policy in Europe

efpia

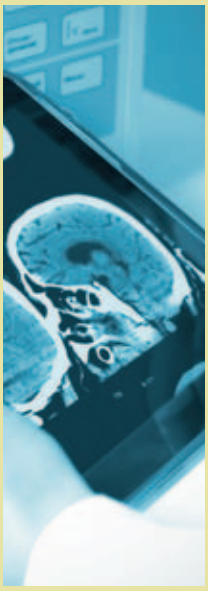
innovative medicines initiative

The Innovative Medicines Initiative: Europe's partnership for health

Diabetes

- 51 milion cases in Europe
- Cost Europe €129 billion in 2014

IMI is investing in 4 projects working to improve diabetes research and develop tailored diabetes treatments for individuals

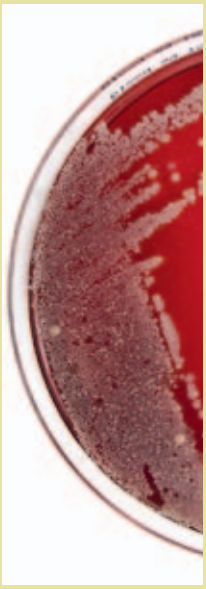


Brain disorders

- Affect one in three Europeans
- Cost €798 billion every year to the European economy
- Drug development takes longer and costs more than other diseases

IMI is investing in research projects addressing Alzheimer's disease.

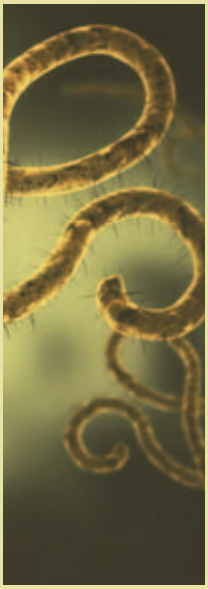
IMI also runs projects on autism spectrum disorder (ASD), schizophrenia, depression and chronic pain.



Antimicrobial resistance

- Kills 25 000 Europeans every year
- Costs €1.5 billion to the European economy annually
- Only 2 new classes of antibiotics developed in the last 30 years

IMI's New Drugs for Bad Bugs programme on antimicrobial resistance tackles the scientific, regulatory and business challenges of antibiotic development.



Ebola

- The current Ebola outbreak has resulted in over 23 000 cases and more than 9 600 deaths
- There are currently no licensed vaccines for Ebola

IMI is investing €215 million in 8 Ebola projects covering vaccine development and manufacture, vaccine uptake, and diagnostics. The projects are part of the wider IMI Ebola+ programme.

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EDITORIAL

Medicines policy in Europe

All European institutions and policymakers maintain that accessible healthcare is a universal right. However, the policies used to fulfill this right vary from a State to another. Costs and benefits, risks and opportunities are analyzed independently and patients are not always at the center of the decision-making. In any case, innovation in this sector has direct positive consequences on the wellbeing of the society and the economy. Unfortunately, the market for these innovations in medicine is imperfect across the continent and governments are feeling the financial pressure to uphold their commitment to access more than ever before. It is under this newfound pressure that the European Union must tackle one of its most successful and complex industries: the pharmaceutical sector.

Access is at the forefront of this debate; Access to innovative medicines for patients, access to Research and Development (R&D) details, access to market information, etc. Conventional initiatives have been taken by the EU as well as member states to accelerate the deployment of medicines. More cooperation, at an earlier time, and with more participation is the foundation of initiatives such as PRIME, STAMP, and Innovative Medicines Initiative (IMI). These initiatives demonstrate the power of the EU to coordinate its state-of-the-art network of private, academic, and institutional partners. However, individual nations have also spearheaded their own initiatives to strengthen their bargaining power in the market and promote transparency in the industry. The Riga Roadmap or France's own Economic Committee for Health Products (CEPS), each a re-envisioning of the negotiations process, are strong examples of national solutions towards a fairer and human-centric market structure. Pricing restricts access to medicines; therefore these negotiations are crucial to the sustainability of the European healthcare system. Indeed, France may join the Belgium-Dutch-Luxembourg alliance to negotiate drug prices together while Germany prefers to remains aloof Secrecy of the process of negotiations is growingly criticized as pharmaceutical companies can easily negotiate discounts and rebates in certain countries and not in others creating a shift of equality in the EU. Differential pricing as a solidarity mechanism in the EU could be one of the long term key solution on those topics.

Medicine policymaking can also benefit from the progress made in technologic coordination within the EU. Although it is clear that the market and its R&D continue to function without much transparency, tools such as the Health Technology Assessment (HTA) help evaluate the true value of its products by progressively defining HTA common EU criterias. Cooperation is slower than expected and some argue that the efforts to streamline analysis of the market benefit the pharmaceutical companies more than patients. Nevertheless, HTA and other tools of analysis allow regulators to pass medicines more efficiently.

The challenge of accepting more innovative and affordable medicines remains, but our ability to identify their value is more and more complex. Patients with unmet medical needs due to poor incentives in innovation or restricted access from high costs have the most to gain from a quality-based approach to policymaking. "Added value", in this case, is not incremental or applied generally to all of society, but rather targeted to those groups without market access such as children with life-threatening diseases or patients of rare and chronic illnesses. The consensus explored by policymakers is that all patients, underrepresented or not, should play a larger role in the development of medicines.

The EU's policy towards medicines is under much scrutiny as costs continue to rise and stories continue to shock the public. The major players of this issue are aware and mobilized to create a new framework for a sustainable model of healthcare in Europe. Although the attitude towards the pharmaceutical industry is mixed, optimism lies with the advances in technology and the progress made in personal and preventive care. This issue of The European Files highlights the core challenges to create comprehensive policy on medicines.

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Assessing health technologies: the added-value of EU cooperation

Vytenis ANDRIUKAITIS
EU Commissioner for Health and Food Safety

Last year the EU celebrated the 50th anniversary of pharmaceutical legislation, which has resulted in one of the safest and most advanced medicine monitoring systems in the world - a system that ensures the safety of our citizens, while simultaneously supporting research and innovation. Celebrations of this important milestone included a conference on EU pharmaceutical legislation to review achievements and explore future perspectives. This edition focuses on 'Medicines policy in Europe' including research into new classes of antibiotics, and their alternatives, as part of the effort to tackle antimicrobial resistance which is a major priority of mine. Another important and relevant topic for the current year is also the EU cooperation on Health Technology Assessment (HTA) on which I would like to develop further.

The 2008 financial crisis, and its aftermath, led to intense scrutiny on public spending in all sectors, including healthcare. During the crisis and the years that followed I was member of the Lithuanian Parliament and subsequently Health Minister for Lithuania. I remember the rallying cries by health advocates – not least myself – to ring-fence health budgets. Access to healthcare is a universal right, which is enshrined in the EU Charter of Fundamental Rights, and any budget cut is therefore inadvisable as the overall cost to society is too high.

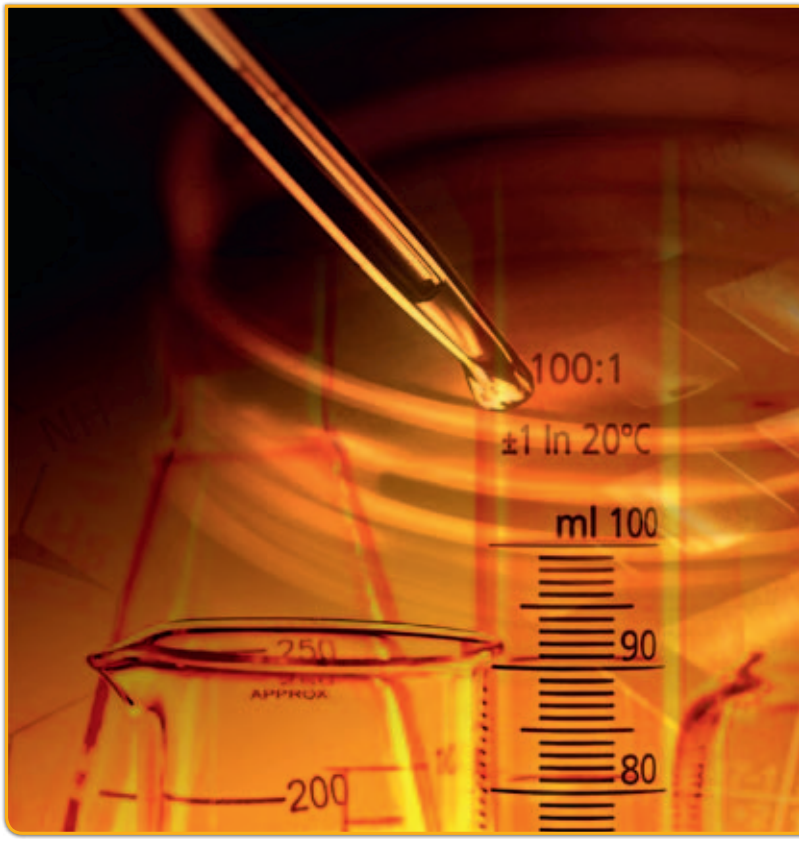
Now as European Health Commissioner, I stand by these assertions more than ever. We can only emerge stronger from the economic crisis if we have a population in good health. I am of course acutely aware that Europe's healthcare systems are under an increasing burden due to - among other things - a combination of an ageing population, a rise in chronic diseases and in multimorbidity. We also live in a world of rapid increase in innovative medicines, medical devices and cutting-edge diagnostic tools - and patients expect to benefit from these advances. Many of these products and therapies are extremely costly, and there is often a high price variation between Member States.

In practice, even if healthcare budgets remain untouched or increase slightly, national authorities need to ensure sustainable health systems so that all healthcare-related tools, be they diagnostic or treatment methods, medical equipment, pharmaceuticals, rehabilitation and prevention methods or even organisational and support systems, are worth the investment.

This is where Health Technology Assessment (HTA) comes in. HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner. It aims at informing decision makers on the formulation of safe and effective health policies that are patient-focused. **HTA answers questions like: Is the technology effective? For whom does it work? What costs are entailed? How well does it work compared to alternative technologies**?

I believe that HTA provides powerful evidence-based instruments for health policy makers and administrators to meet the aforementioned challenges. HTA assessments enable them to select the new effective technologies, rejecting those not providing added value, and stopping using obsolete ones.

As an instrument to promote efficiency and effectiveness of healthcare is a necessary element for the modernisation of health systems. **I am convinced that pan-EU cooperation on HTA will bring real added value to all countries, through the pooling of resources, exchange of expertise, and the avoidance of duplication in the assessments of the same product or intervention in different Member States**. In particular



for medicinal products but also medical devices, multiple assessments impose a high cost and loss of time on the industry which needs to submit its application multiple times, according to different requirements. For Member States separate and varying assessments mean duplication of work, and waste of scarce expert resources. And for patients and industry there is more uncertainty on the outcome and questions about quality. So, in practice, Member States seldom assess technologies other than pharmaceuticals due to the resource constraints. EU cooperation on HTA and synergies between European and national activities would enable to solve this situation.

We are obviously not starting from scratch. Back in 2013, a voluntary EU-wide network on HTA composed of national HTA bodies or agencies was set up. It built on preparatory work that provided us - and will continue to provide us - with a solid knowledge base notably on areas where attention is needed in producing EU level reports, as well as on the reusability of EU assessment reports at national level.

Current EU cooperation on HTA has so far led to poor use of the joint EU assessments by Member States. A discussion paper adopted by the HTA Network last year actually calls for further reuse of joint reports at national level. This discussion document suggests a sustainable long-term solution, which includes legislative and non-legislative measures, and outlines the objectives, technology coverage, coordination ambition, level of EU financial support, and governance arrangements.

We are therefore at a turning point. To anticipate future challenges, I believe we should put in place a more permanent structure to replace current cooperation between Member States. HTA deserves greater attention at European level as the benefits of such a sustainable EU cooperation on HTA are numerous. It will promote convergence of approaches on how to carry out health technology assessments, ensure better use of resources in HTA production, and lead to consistency in assessment outcomes. **For patients, it should in the end ensure timely access to innovative health technologies and treatments.** It will also contribute to the functioning of the internal market for health products, as indicated in the recent EU Single Market Strategy, and to the sustainability of health care systems.

Last year, I have proposed to and succeeded in including the launch of preparatory work on HTA in the 2016 Commission's annual Work Programme. This is a crucial milestone. The Commission has supported voluntary cooperation in this area for more than twenty years. In 2016, it is now time to build on our achievements and bring fresh impetus to the efficient use of HTA resources in Europe. We are now working on an impact assessment to carefully assess various options linked to the setting up of this permanent structure.

From my perspective, the greatest benefit of EU cooperation on HTA is improved health for European citizens thanks to assessments of health technologies according to the best methods available. The Commission's work programme aims to ensure progress on actions which will make a positive difference for Europeans. I believe that EU-cooperation on HTA fits this description perfectly, and that it will pay dividends for us all.

Better health for all – one person at a time

Carlos MOEDAS
Commissioner for Research, Science and Innovation

Hippocrates the father of Western medicine famously noted, *"it is far more important to know what person the disease has than what disease the person has"*. He was right. Any doctor will tell you that patients suffering from what seems to be the same disease will react very differently to the same treatment. Looking only at the disease and not at the person is bound to lead a physician astray.

Our healthcare systems, however, are still mostly geared towards "one-size-fits-all" approaches. They treat the disease or symptoms instead of the person. They try and often fail, so they have to try again. For this reason, several common medicines do not work in many of the patients that they are supposed to treat, leading to poor results, unnecessary suffering and high costs. With an ageing population and a growing number of chronic diseases, Europe needs to change its healthcare paradigm.

Personalised medicine holds the promise of bringing about this change.

Personalised medicine places the patient front and centre. It looks at the patient's molecular profile, environment and lifestyle to decide what treatment strategy will work best. This approach, which integrates information from multiple sources, can make healthcare smarter, better and more cost-efficient. The vision driving this development is that healthcare should become proactive instead of reactive. With better knowledge of the mechanisms governing health and disease, predicting and preventing ailments will become even more important elements of the healthcare equation, helping to reduce healthcare costs and allow people to live healthier and more productive lives.

Jobs, growth and investment

research and innovation is driving progress in this area and thanks to a number of factors Europe is at the forefront. Personalised medicine is a vanguard area of healthcare and health research. It uses many new technologies and innovations that can create jobs and growth in the life sciences sectors.

The market opportunities in the area go beyond medicines and diagnostic devices. They include demand for products such as high-tech storage and data-sharing, as well as low-tech devices and services aimed at heightening awareness of personal health risks.

Investing in personalised medicine research therefore contributes to the European Commission's objective to create more jobs and higher growth in Europe.

Open science, open innovation

personalised medicine is one of the main health research priorities of Horizon 2020, the EU's funding programme for research and innovation. A large part of the budget of over €2 billion for the first years of the Health, Demographic Change and Wellbeing challenge has been dedicated to research aiming to personalise health and care. For example, two pilot projects with a combined budget of around €30 million are starting this year, which aim to trial personalised medicine approaches in existing healthcare settings. The projects will also evaluate how these new approaches bring value to healthcare systems and patients.

The Luxembourg EU Presidency made personalised medicine a priority area. The Council conclusions on "*personalised medicine for patients*" published in December 2015 is a welcome development. Beyond Europe, both China and the USA are launching ambitious programmes.

The research agenda of the Innovative Medicines Initiative (IMI), the world's largest public-private partnership in life sciences, rests on the fundamentals of personalised treatments. One example is EU AIMS, a €37 million project aiming to explore the biological causes of autism, with a view to developing personalised treatments.

Prioritising a cutting-edge field like personalised medicine can help policy makers to design the right framework conditions for innovation - our continued work on better regulation can be informed by the advances in this area. We need to make sure that there are no unnecessary barriers blocking the development of innovative personalised medicine treatments and approaches.

Open to the world

despite our efforts and promising developments in some areas of personalised medicine we need to do more.

That is why the Commission together with European research funding agencies and policy makers are working to set up a collaboration that will be called the International Consortium for Personalised Medicine (IC PerMed).

IC PerMed's aim will be to establish Europe as a global leader in personalised medicine research and to further develop the science base needed to bring about change. It will take a holistic approach to this field and will develop a roadmap to tackle research challenges from the scientist's bench to the patient's bedside. After an initial phase focusing on Europe the initiative will be ready to engage with other organisations across the globe.

This new initiative will be officially launched at the Personalised Medicine Conference 2016 here in Brussels on 1-2 June. I look forward to welcoming you to this conference where the IC PerMed roadmap will be presented through engaging sessions and discussions.

Better health for all is more than a catchphrase. It is the vision that guides the Commission's health research funding and policy work. Let's always remember that better health for all means better health one person at a time.

Note: Read more about the Personalised Medicine Conference 2016 on http://ec.europa.eu/permed2016

How does one ensure access to medicines at affordable prices?

Marisol TOURAINE
French Minister of Social Affairs and Health

Medicine policy is a key component of our social protection system. It aims at ensuring access to medicines to any patient in need while keeping health expenditures under control.

It is vital to guarantee that the sick have access to medicines. In order to allow fast access to innovative medicines France has set up an early access mechanism: the Temporary Use Authorisation (ATU). This unique mechanism enables patients to benefit from the most innovative medicines even before they are granted marketing authorisation, provided however that they meet strict security conditions.

Ensuring the financial sustainability of our system is equally paramount. In France, the regulation of the medicinal products sector is based upon a convention between the State and the health industries, which seek to conciliate the purposes of industrial development and the demand for public health expenditures control. Indeed, in France, medicine coverage depends upon national solidarity. Therefore, medicine-related expenditures are an integral part of the National Health Insurance Expenditure Objective (ONDAM). This regulatory tool, championed by the OECD, determines the level of health insurance expenditures on an annual basis. Where there is a risk that this objective will be exceeded, mechanisms are triggered in order to reduce the overall spending envelope.

The coverage of medicines by national solidarity is conditional on a scientific and medico-economic assessment being carried out by an independent agency, the French National Authority for Health (HAS). This assessment also provides the basis for negotiating the price of medicines with the sector's manufacturers, conducted by the Economic Committee for Health Products (CEPS). The CEPS is a body that comprises representatives from various ministries (Health and Social security, Economy and Indust ry) as well as compulsory and complementary health insurance representatives. It plays a major role in implementing conventional policy. Medicine prices in France are a reference for a number of countries across the globe, which no doubt reflects the virtuous circle that has been put in place in our country.

Furthermore, the CEPS plays a central role in regulating the medicines sector. Allowing access to the latest medicines entails ensuring the dynamic management of the prices of the medicines available in the "basket of care". Added to this is a macro-economic regulation supported by a specific mechanism, the safeguard clause, which aims at protecting health insurance expenditures from an overly fast increase in medicine-related expenditures in relation to the expected trend. Any exceeding should largely be compensated for by pharmaceutical laboratories.

This process has nevertheless shown some limitations, namely with medicines intended for the treatment of hepatitis C virus infections. Given the prices charged by manufacturers and the great number of patients requiring treatment, a risk of severe imbalances in health expenditures was to be feared. In order to address and remedy this exceptional situation the French government has decided to put in place a specific regulatory mechanism for these products. This measure allowed controlling the impact of the new treatments on medicine expenditures, while permitting a very fast access to these products.

While we have managed to promptly cover treatments for hepatitis C, the upcoming arrival of many other therapeutic innovations, especially in the field of cancer, as well as the continuous rise in prices demanded by the pharmaceutical laboratories poses a threat in terms of access to those innovative medicines. And we simply cannot accept it. The benefits of these innovations for a large number of patients cannot be called into question because of their high price tags. This cannot be envisaged neither for public authorities and manufactures nor for our fellow citizens. This matter is currently at the centre of our concerns. The answer to this challenge is to be found beyond our borders. We need to shift the lines. All of this was conveyed in the initiative launched by France at the Employment, Social Policy, Health and Consumer Affairs Council meeting in June 2014 and which had aroused the immediate interest of 14 States. Its aim is not to plan a global negotiation of medicine prices, as each country has its own organisation arrangements and medicine policy. However, it is becoming essential to reinforce cross-country cooperation in order to find common solutions.

It has now become urgent to engage medicine manufacturers and to find sustainable solutions in order to preserve our funding models. We share common interests: guaranteeing the fundamental right of access to medicines for all patients and supporting long-term innovation in the health care sector.

Setting the right incentives for an optimal development of pediatric medicines

Françoise GROSSETETE
MEP, (Vice-President of the EPP Group)
Member of the ENVI committee

The Paediatric Regulation adopted in 2007, and in which I have been greatly involved as a Rapporteur, has been a big step forward to push industry to consider research and development of paediatric drugs in Europe. One of its main achievements is to have made Paediatric Investigation Plans (PIP) mandatory in drug development. The Paediatric Regulation stipulates indeed that companies have to evaluate every new product they are developing for adults, to determine whether it has potential for the treatment of children.

Despite those progresses, the current Regulation has unfortunately not fully met expectations and has had very little impact on the availability of treatment for paediatric cancers, with only one oncology drug developed since the Regulation was put in place. And yet, we are in a situation of emergency.

Today in Europe, children with cancer and other life-threatening diseases are being denied access to potentially life-saving treatments. This is a public health issue of prime importance. Cancer remains the leading cause of death by disease in children across Europe. Each year, 35,000 children and adolescents are diagnosed with leukaemia or malignant solid tumours and 6000 of them die. Of the survivors, 40% will be left with severe long term side-effects which impact their daily life.

For some of those conditions with a poor prognosis, only very limited improvements in treatments for children have been seen in recent decades. The problem is not only medical but economic. As childhood cancers are comparatively rare, they have been largely neglected as they do not represent a broad enough market for drug manufacturers, who still consider adults their main customer base.

As a result, today, European children still have no access to evaluated, safe and innovative medicines. The problem can be said to be threefold:

First, the system of Paediatric Investigation Plans (PIP) is currently too rigid and slow moving. To the aim of evaluating the potential adaptability of adults' drug to children, pharma companies have to submit a PIP to the European Medicine Agency in the first stage of research. However, research in children is currently difficult to conduct, due to very rigid rules, the ethical difficulty of submitting children to clinical trials, and the fact that children only constitute a very small population of those affected by rare illnesses. Therefore, recruiting young patients to take part in clinical trials amount to a true challenge.

If the industry is to be fully engaged, it must be given reasons to do so. Therefore, a more effective system of incentives and sanctions must be put in place to encourage the industry to engage in paediatric research, on the model of the *Creating Hope Act* adopted in the United States in 2012. A segmented reward approach under the form of extensions of market exclusivity could be a possible solution. In the rare diseases area, I could see how extended periods of market exclusivity could act as a strong incentive for innovation. Clinical trial sponsors should also be encouraged to be more flexible about including paediatric patients in adult trials, where this would be beneficial to paediatric research.

Second, there are simply too many waivers. Specifically, when it is determined that the drug being researched is intended for the treatment of a disease that only occurs in adults, companies can apply to have the PIP waived. This possibility is largely abused, even taking into account the review of the class waiver list by EMA in July 2015. More than 60% of PIPs are associated with waivers and all possible procedures are used to delay the paediatric development. For example, in the first five years of the Regulation, twenty six drugs with potential application to childhood cancers were approved for adult marketing, but over half of these received a paediatric waiver.

Third, the processing time of files is problematic, with many cases still awaiting evaluation. We must accelerate the process in the EMA as well as with national agencies. We know that some drugs for adults can be active at a molecular level in certain childhood diseases. In cancer, for example, there are important biological connections between adult and childhood malignancies. Therefore, I would propose replacing the current waiver system with one that instead examines the mechanism of action of the drug.

Facing these stumbling blocks, the Commission has decided to issue in 2017 a report on the implementation of the Paediatric Regulation. I do believe, however, that we cannot afford to wait 2017 to take action when we already have a clear picture of the loopholes of the current legislation. Not when so many children are suffering because treatments either do not exist or those that do often have severe, long-lasting side-effects. A full review of the Regulation may not necessarily be the best tool to move forward, but the Commission should at the very least immediately evaluate the situation and the application of the Paediatric Regulation, in order to be able to correct it as soon as possible.

Together with other colleagues from the Parliament, I have decided to build the pressure on the Commission and we have recently published an open letter to Commissioner Andriukaitis to let him know about our determination. Supported by a European network called "Unite2cure", which is composed of numerous parents' organizations, NGOs, doctors and researchers, we have started a battle to make a real change for young patients victim of paediatric pathologies. Europe should lead the way, not lag behind. Time for action is now.

Antimicrobial resistance - Our window of opportunity

Xavier PRATS MONNE

Director General, DG Health and Food Safety (SANTE), European Commission

One of the mainstays of scientific lore is the story of the unlikely chain of events that led to the discovery of penicillin in 1928. A window, left open in a lab, made it possible for a mould carried in by the breeze to take root on a dirty petri dish. Staphylococcus bacteria covered the dish overnight, except for a circular area around the mould. Alexander Fleming's understanding of what this "halo" meant was his "Eureka" moment. He correctly deduced that the mould released a substance that inhibited the growth of the bacteria and in an instant brought medicine forward a hundred years. Until today.

Today we are facing the exact reversal of that moment. We have reached the point when, due to use and abuse of antibiotics over the years, we have allowed bacteria to develop resistance to nearly all of our antibiotics. Today in Europe alone 25,000 people die because of this and our already overburdened healthcare systems are incurring an extra €1.5 billion in costs due to antimicrobial resistance.

The sad thing was that we knew this from the start. Alexander Fleming, speaking in his Nobel Prize acceptance speech in 1945 said *"The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to non-lethal quantities of the drug, make them resistant."*

This resistance predicted 70 years ago by the man who discovered the first antibiotic, is upon us and we have to take significant measures to fight it. Europe has been at the forefront in the fight against antibiotic resistance for the past 15 years. Over the last five years we have launched and adhered to a pioneering Action Plan covering both the human and the veterinary aspects of the problem. This 'one health' approach, strengthening the prevention and control of antimicrobial resistance across all sectors, is the cornerstone of EU policy.

The Action Plan has been evaluated and the main results were presented earlier this month at the Ministerial meeting organised by the Dutch EU Presidency. The outcome will contribute to further policy developments in 2016.

The Action Plan has clearly been proof of the political commitment to tackling antimicrobial resistance in the EU. It addressed the relevant issues, resulting in more effective coordination, and producing tangible results in areas like prudent use and addressing infections in both animals and humans alike.

But this is not enough: the Commission is ready for a qualitative leap forward, to support Member States in their national efforts, and establish the EU as a best practice region in this field so as to lead the way in the global fight against antimicrobial resistance. We can help in many ways: by providing support to the development of the national action plans and ensuring that the necessary expertise is available to all; by putting in place in the coming months a "One-Health' AMR network", as a forum bringing together Member State experts from both the veterinary and human health domains as well as actors from environmental sector. The discussions in this One-Heath network could lead to the establishment of harmonised guidelines on prudent use of antimicrobials in the human health sector, to complement the already existing guidelines on prudent use in the veterinary sector. We could engage with the pharmaceutical industry to fight against antimicrobial resistance and foster awareness among public authorities and healthcare professionals through better training.

All these initiatives must be sustained by research and innovation into better ways of diagnosing resistance, finding alternatives to antimicrobials and new pathways that facilitate quicker access for patients to new medicines. These are not mere wishes but an actual, tangible, results-based approach that we plan to put into action in the months and years to come.

We are also aware that, very much like climate change, antimicrobial resistance is a global problem whose solution lies in bringing about a global political will to succeed. That is why, coupled with these initiatives, we are shaping the EU's role at international level so as to bring the world's focus on this problem.

Europe's credibility as leaders in the field is cemented through the various measures taken over the past years, such as the ban on the use of antibiotics to promote growth in animals. Our Action Plan has also served as the basis for the Global Action Plan adopted by the World Health Organisation in 2015.

The European Commission will therefore reinforce its engagement with the World Health Organisation, offering our expertise to ensure the success of the Global Action Plan. The EU should be one of the driving forces in the preparations for the high-level event on antimicrobial resistance at the United Nations General Assembly in September 2016. We will also enhance our collaboration with the OECD to invest more on knowing the economic and societal impacts of antimicrobial resistance. And antimicrobial resistance should be high on the EU agenda when negotiating bilateral cooperation and trade agreements, and in our dialogue with neighbours who are seeking enlargement or are part of our neighbourhood policy.

The challenge in front of us is huge and the effort we put in has to be equal to the task. We have a window of opportunity ahead of us, which, very much like the window in Fleming's lab so many years ago, has been left open. Whether we can grasp this opportunity will depend very much on the effort we put in, on the sacrifices we make and on the collective goodwill of nations and individuals alike.

Patients at the core - steering research and development towards addressing unmet medical needs

Guido RASI
EMA Executive Director

The system of medicines development and authorisation is currently undergoing a significant transformation. Scientific advancements in the area of molecular biology made over the last 40 years have provided us with valuable insights on the mechanisms behind the development of diseases. This has created huge opportunities for the development of human medicines. At the same time, the sustainability of healthcare systems across the European Union (EU) is under threat, due to rising costs, an ageing population with more complex healthcare needs and a continuous squeeze on public finances.

Pharmaceutical companies will have to find new models of medicines development that work in this new environment.

But also we, the medicines regulators, need new approaches if we want to ensure that medical innovation is translated into safe and effective treatments that address patients' unmet medical needs and their demands for timely access to new life-saving treatments.

At the European Medicines Agency (EMA) we have launched a number of initiatives that stimulate innovation, optimise development and contribute to patients' quicker access to new medicines. In this article we outline two of these initiatives. The first one, EMA's new priority medicines scheme, PRIME, aims to make better use of the existing regulatory tools in Europe and promotes early dialogue between the Agency and medicine developers to strengthen clinical trial designs and enable accelerated assessment of new medicines which target major public health needs. The second initiative, our adaptive pathways pilot project, explores a new concept of medicine development, especially for medicines that address small patient populations.

EMA's Priority Medicines Scheme

In March this year, EMA launched a new initiative called PRIME. With this initiative we want to do our part to allow promising medicines to reach patients earlier. If a new medicine can show the potential to either treat patients who currently have no treatment options, or provides a major therapeutic advantage over existing treatments, we consider this to be a priority medicine, hence the name of the scheme. These medicines could be accepted for PRIME and their developers would receive early and enhanced scientific and regulatory support in order to optimise the generation of robust data. Patients, on the other hand, would benefit from PRIME because they would have access to therapies that could significantly improve their quality of life as early as possible.

With PRIME's focus on medicines that address unmet medical needs, EMA hopes to encourage developers to direct their resources to those candidate medicines that are likely to make a real difference to patients' lives.

However, PRIME is about more than providing extra support to medicine developers. Through the scheme we aim to also reach out to those who are not necessarily familiar with the regulatory requirements but who play a key role in medicine innovation. These could be start-ups, academic spin-offs, and other small companies that often struggle to bring an innovative invention or new discovery forward to drug development. We want to help these key stakeholders translate promising research into the development and authorisation of new medicines for patients.

Adaptive pathways – a new concept of medicine development

Already since 2014, EMA has been exploring a new concept of medicine development that

would allow patients who have no or only limited treatments for their disease to benefit from scientific progress as early as possible, without compromising their health and wellbeing.

Under the so-called adaptive pathways approach, the development program for a medicine is restructured and entails an early approval often based on small initial clinical studies to allow a limited population with a high unmet medical need to access the new medicine. In real life, that is when the medicines are already used, additional data are collected.

It is important to note that the standards for the evaluation of the benefits and risks under adaptive pathways remain the same as for any other medicine. Approval will only be granted if it is clearly demonstrated that the benefits of the medicine in the treatment of the target population outweigh its risks.

Generating and assessing data on the benefits and risks of the medicine continuously in a real life setting is one of the key pillars of this approach. Clinical trials are planned prospectively and as more data become available, regulators can adjust the conditions of use of the medicine by either restricting or expanding the marketing authorisation.

Another pillar of the approach is the involvement of all stakeholders who provide input to all elements of the process from the early stages of medicine development. Under adaptive pathways, clinical medicine development, licensing, reimbursement, use in clinical practice, and monitoring of treatment outcomes are viewed as a continuum and should therefore to the extent possible, be planned in a prospective and integrated way.

In order to explore how the adaptive pathways approach might work in the real world, with real medicines, EMA launched a pilot project in March 2014. This pilot, which is still ongoing, provides a framework for open and informal dialogue between regulators, pharmaceutical companies, health technology assessment bodies, patients and healthcare professionals. They can discuss challenges and options in a 'safe harbour' environment and consider detailed technical and scientific questions based on concrete examples.

Early dialogue between regulator and medicines developers

PRIME and adaptive pathways are two important schemes that underline the Agency's commitment to patients' welfare. Early dialogue between EMA and developers is central to both of them and EMA's scientific advice programme is the Agency's main platform for this.

EMA's experience over the last decade has shown that early scientific advice is key for a robust development program that can protect patients but also helps to speed up their access to medicines. The Agency is encouraging medicine developers to seek advice early in the development of a medicine when changes can be made more easily and at a lower cost compared to later stages. Scientific advice benefits patients as it promotes the generation of robust data and strengthens clinical trial design. Overall, these efforts, that are in line with the European Commission's priorities and are carried forward in close cooperation with the network of national competent authorities in Europe, protect patients and ultimately help to maintain public confidence in the integrity of the system of medicine development in the EU and beyond.

EU approaches to pricing: a realistic option to deliver better and faster patient access?

Philippe DE BACKER

MEP (Group EPP), Member of the Committee on Industry, Research and Energy

"Access to affordable healthcare isn't a privilege; it's a right" said Barack Obama when defending his Obamacare plan that revolutionised the US health care landscape. But is that so? Healthcare demand is infinite, while supply is per definition limited. Maybe we have to realise that we cannot guarantee near free unlimited healthcare services for everyone at all times. It sounds cold, but it shouldn't be. Giving access for me boils down to using transparent criteria and applying an evidence based approach.

Access to healthcare in general, and innovative treatments in particular, also depend on developments in the larger healthcare industry, and those developments are going faster and faster. We constantly see new drugs being developed; we see a larger focus and importance of personalized medicines and the integration of personal data in designing therapies, to only name a few. These developments will require another way of thinking about pricing and access. The question for policymakers will be how we make sure that these novelties make it to the market and to the patient as fast as possible and at the right price. Another question is to what extent is it remains relevant for member states to hang on to their own different pricing systems in a wider European context, be it free pricing, external reference pricing, internal pricing or value-based pricing.

This is where I believe changes are required in order to exploit the full potential of a larger European scale and stronger bargaining power through procedural harmonisation. Many market players are still very reluctant (to say the least) when I plead for more cross-border cooperation or a stronger coordinating role for the European Commission. We are currently already seeing these kinds of joint systems being started in a bottom-up approach. Belgium, the Netherlands and Luxemburg have initiated a joint purchasing scheme and other member states are considering joining. This initiative is mainly aimed at bringing down the cost for orphan drugs, and facilitating access to these drugs for people suffering from rare diseases. Next to this, they are also going way beyond solely agreeing on jointly negotiating with the pharmaceutical industry. They also envisage exchanging data, share registries and coordinate assessment methodologies. This is not only beneficial for the patients and the healthcare budget by having faster access and lower prices, but pharmaceutical companies will also gain from only having to submit one dossier and having direct access to a larger patient population.

Next to different pricing systems, also the different HTA systems differ greatly between the member states. The EUnetHTA has, which was established following a 2013 Commission decision based on the 2011 Cross-border health Directive, has already make some first steps in preparing the ground for a more common approach to HTA. So far however, it mainly has been a theoretical exercise with a focus on developing theoretical models for possible progress in this field. Except for some member states that have expressed an interest in a closer cooperation, most member states still remain reluctant to do so. On the industry side we have seen some movement in the right direction. They are willing to discuss closer cooperation with regards to the therapeutic added value of a new treatment, but many still don't see any benefit in member states jointly addressing access issues.

The moment we decide to do this together to me is also the moment where we should decide to it differently, and better. This is where I believe we should take the step to apply innovative pricing mechanisms at EU level, and we have make a shift to accountability payment models based on results. I think in a first step we should move from volume to value, to a situation where treatments will be assessed on clearly demonstrable benefits and patient outcomes. These value based pricing models should align economic incentives for innovation with public health priorities.

But things are moving slowly, and that is too bad. Because the way we access our medicine will become an ever more important issue in this debate. It is commonly known that public budgets are under serious strain since the financial and subsequent economic crisis hit Europe. Healthcare budgets are also increasingly challenged due to demographic changes, with our ageing population as main culprit. At the same time we know we should never waste a good crisis, and that these external pressures could be a good ground for member states to go from theory to practice.

Although access is indeed a major issue, we shouldn't stop there. We also need to look at the rest of the value chain. An increased focus on early diagnosis and more attention to prevention can lead to significant gains both for patients and healthcare budgets.

I believe that we should stop making incremental changes to our healthcare systems and stop aiming at keeping its design because it is no longer fit for service. Closer European cooperation, both on purchasing and HTA can lead the way for a larger overhaul. This in turn should create a window of opportunity to take on board more innovative ways of looking at pricing, taking into account the value in the larger sense of a new treatment. We shouldn't do it because we have to, we should do it because it makes a lot of sense for the patient, for the industry and for ensuring the sustainability of our healthcare systems.

The need for HTA throughout a medicine's lifecycle

Lieven ANNEMANS

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It is generally accepted that European healthcare systems need innovative medicines of high value to help reduce morbidity and mortality, and to increase healthy life expectancy in the EU. Medicines are considered of high value if they offer a benefit to patients (for instance substantial QoL and/or life expectancy improvement) and/or to society (for instance productivity gains, efficiency gains), especially in areas of high medical need (as reflected by the severity of disease or the life threatening nature of a disease).

But high value does not necessarily mean 'value for money'. The challenge is to set a price and reimbursement level that rewards the value correctly, hence leading to acceptable value for money. We need health technology assessment (HTA) to inform policy makers about the value and the value for money of innovative medicines within our healthcare systems. In general HTA is used as key input for pricing and reimbursement decisions. However HTA should play a role in the three key phases of a medicine's lifecycle, the development phase, the market access phase and the market usage phase.

During the development phase, medicines should already be assessed for their potential cost-effectiveness, based on the target product profile. This is mostly referred to as 'early economic evaluations'. Typically this activity must take place before undertaking a phase III trial. Indeed, the information from these evaluations can guide further prioritisation and development. The early evaluation may for instance indicate that the medicine will likely only be cost-effective in high risk patients, or only in second line treatment after failure of first line.

Another activity during the development phase is related to early dialogues and joint advice, whereby the idea is that the European Medicines Agency (EMA) and the HTA bodies can advise companies about the possible methodological and strategic choices in the clinical development of their innovations, in order to be better prepared for the market access phase. .

During the market access phase the submission is prepared for obtaining price and reimbursement approval for the medicine. Here, a full Health Technology Assessment (HTA), looking at all clinical, economic, ethical, and organisational consequences of a new medicine is in principle to be applied. Yet, in the past (and still today) a lot of duplication in efforts has been observed. HTA bodies undertake the same analysis as already done by the EMA and all member states deploy their own analyses and assessments. Fortunately, there is an encouraging trend within the EU towards more joint assessment of at least the clinical value of medicines. Moreover, several countries can deal with HTA more efficiently by using HTA results of other member states with more HTA capacity.

An important challenge during the market access challenge is the uncertainty about the value for money of medicines. In fact there are four key types of uncertainties:

- Uncertainty about the actual effects of the medicine (will response rates be as good in real practice?);
- Uncertainty about the consequences of this effect (for instance the relationship between an intermediate endpoint such as cholesterol level and hard endpoints such as heart disease);
- Uncertainty about the correct use; and
- Uncertainty about the market penetration of the medicine

All have an impact on the cost-effectiveness and/or the affordability of medicines. It is obvious that decisions need to be taken in the presence of these uncertainties. Hence, there is a need to develop better risk sharing agreements dealing with these uncertainties. Real life practice data collection, for instance in registries, and better use of electronic health records, is needed to observe the real life practice outcomes of medicines.

Hence, once medicines have obtained reimbursement, additional HTA activity is required during the market usage phase of the medicine's lifecycle. At a given point in time there is a need for validation of the predicted benefits, in other words for verification and re-assessment of the value and value for money of the innovative medicine.

Ideally, the format and methodology behind the datasets should be based on their goals and not vice versa. Today, too often, datasets are created without a clear proactive view on the ultimate goals of the uses of this data. The research question (what needs to be the subject of verification?) must be clear from the start. Furthermore these datasets should be more harmonised and standardised in order to deliver similar and comparable data in Europe allowing interpretation on a larger scale, while ensuring the necessary protection of privacy. The ownership and financing of such datasets needs to be worked out and there may be a role for Public Private Partnerships in their establishment and operation.

In the future, the full introduction of electronic patient records containing all health related data of European citizens is essential. Health informatics systems will not only be crucial in the development phase of medicines but also within the market usage challenge to observe and guide their appropriate use and effectiveness. Current initiatives to establish registries still requires a lot of work, and, in parallel, greater governance is needed to speed up this process towards full capacity health informatics systems.

Is Conditional Marketing Authorisation (CMA) a Procedure of exception or a "tag" for Innovation?

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Table 1: EMA statistics published in Dec. 2015

	2012	2013	2014	2015†
Positive opinions	57	79	81	**84**
Opinions recommending conditional marketing authorisation**	3	4	4	**2**
Opinions under exceptional circumstances**	0	3	1	**3**
Negative opinions	8	7	4	**3**
Opinions after accelerated assessment**	1	5	7	**5**

** Included in the figures for positive opinions.

† Figures for the current year are cumulative, year to date. Figures for preceding years are totals for the year.

In 2006, the Commission Regulation (EC) 507/2006 was adopted enforcing the legal basis for conditional approval (CMA). This procedure was implemented in the European regulatory system to allow patient's early access for certain categories of medicinal products with the potential to address high unmet medical needs in seriously debilitating, life-threatening, or rare diseases.

CMA may be granted for medicines on the basis of surrogate markers and/or "*less comprehensive clinical data referring to the safety and efficacy than usually expected, if all the following requirements are met: (a) the risk-benefit balance of the medicinal product is positive; (b) it is likely that the applicant will be in a position to provide the comprehensive clinical data under the specific legal obligations; (c) unmet medical needs will be fulfilled; (d) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required*"[1]. A CMA is valid for 1 year and may be renewed annually as long as the benefit–risk remains positive at each renewal, a safeguard against defaulting to follow the post-marketing requirements. The table below shows that less than 5% of the yearly procedures involved CMA.

In the US, early access to innovative therapies is a more common practice with flexibility and multiple choices on the way forward. Among the 45 novel drugs approved by the Food and Drugs Administration (FDA) in 2015, 14 (31%) were designated as Fast-Track; 10 (22%) were designated as Breakthrough therapies, 24 (53%) had a Priority Review and 6 (13% vs. 20% in 2014) were approved under FDA's Accelerated Approval program (AA). This latter procedure is similar to the EU CMA as both systems allow for an approval based on surrogate endpoints and early submission during drug development.

The two major differences between these procedures are (a) the requirement for annual re-assessment of benefit-risk and (b) the EU regulation's with financial penalties in case of non-compliance with obligations agreed during the CMA. Those are giving a "repressive vision" to the procedure.

Another important difference is that in Europe, CMA can only be applied to initial marketing authorisations, whereas in US, AA can also be used for "variations" (the efficacy supplements in US) to facilitate early access to extensions of the drug's use in a new therapeutic indication. This would ease the accumulation of evidence during the lifecycle of the product.

A report[2] published in 2014 describes an important gap between the way the CMA procedure is used (see below) and its legislative intent. While EMA[3] reviewed its guideline on CMA, it is important to agree on new ways for CMA to be a "tag" for innovation instead of a rescue option for a dossier not sufficiently documented.

CMA is a necessity for a future iterative decision-making to an efficient adaptive pathway to early access to the patient.

Any Regulatory Agency needs to find the right balance between a timely access to new medicines and the requirement for extensive data supporting their benefits / risks assessment in a public health context. Regulatory paths were implemented to allow early access to medicines and the choice of the procedure dependents on the disease and its unmet medical need, as well as the technology of the product. The greater the severity of the disease, the more uncertainties patients may be ready to accept provided efficacy is demonstrated. A fair balance is also needed between an optimised regulatory path to expedite approval of high-value drugs and an increasingly risk-averse regulatory environment coupled with rising drug development costs.

In the context of complex pharmaceutical development (advanced therapy with manufacturing steps, long time to reach the main primary end-point, heterogeneous populations,...), a continuum of research steps with an iterative decision-making process is needed to integrate new data in an on-going benefit-risk assessment. The new pharmacovigilance tools such as registries, or post-authorisation efficacy/safety studies (PASS / PAES) have opened new options to accumulate knowledge whilst properly managing uncertainties.

1 Article 4 of the Commission Regulation 507/2006/EC

2 Escher Report : http://escher.tipharma.com/fileadmin/media-archive/escher/Reports/Escher_report_IA.pdf

3 Updated CMA Guideline http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500202774.pdf

A positive CMA vision is needed to boost innovation.

The use of CMA as a "rescue" process is questioning the need of the procedure!

Because of the limitation of the data available when CMA is granted, , the procedure takes a longer review times (513 versus 390 days under regular approval) and products are approved with less consensus vote (55% versus 87% usually). In most cases the CMA was used to "rescue" the product (CMA proposed by EMA at D180 end of the procedure) and only in two cases, companies were using CMA by request to EMA with a pre-planned stepwise approach (ESCHER Report)[2]. Accelerated assessment were never used in combination with CMA.

Early dialogue with the Agency on proactive scenario planning to include future steps of evidence generation and uncertainty management would facilitate the procedure.

The use of CMA is questioning the level of uncertainties in the decision-making.

The negative perception of CMA is linked to the limited amount of initial data submitted based on the use of surrogate end-points and exploratory studies, which may be seen by other Stakeholders (HTA, payers, physicians, academicians, ...) as not strong enough to justify their decisions following the regulatory approval. One may question certainty and criteria for the decision taken by the regulators, and any subsequent decision-making may be impacted by these uncertainties.

A further criticism regards the safety judgement, in particular the rare serious adverse events. Studies assessing the incidence of post-approval safety-related measures (e.g. new warnings in the label and communications to healthcare professionals) taken for cancer drugs approved under CMA remained inconclusive. Despite the limited safety data, there[4] was no special safety issue associated with the use of this pathway. Drugs approved under CMA did not lead to more safety related withdrawals or increased risk communication to prescribers after usage for some time after entering the market[5].

All Stakeholders would need to accept and manage uncertainties as part of the generation evidence, benefit/risk and through each decision making time.

EU involves centralised licensing decisions by regulators transferred to the next national HTA/pricing decisions with differences in assessment criteria and evidence requirements resulting in divergent decisions.

The level of evidence included in CMA dossier may challenge the decision-making on value and effectiveness of the product needed for the HTA and pricing / reimbursement. Industry have experienced discrepant decisions across Member States with some HTA bodies including the CMA in a high unmet medical need and innovative context while others having a precautionary reluctance to pay for uncertainty. The questions are: is it a payment for results/performance or for public health? What is the value/the need of the product for the patient? With the CMA procedure including legal obligations with generation of new data, a flexible and integrative approach is needed, i.e. an iterative pathway to adjust depending on the new evidences provided.

An efficient system with a fully translatable decision across all Member states needs a close cooperation between regulatory and other stakeholders (HTA, payers, patients...) to ensure an agreement on which product may fulfil a high unmet medical need, and at which level of evidence. The following data generation for an informed iterative decision is to be viewed by all as a normal pathway.

An early, engaged and collaborative discussion between all stakeholders on the iterative development plan should recognise the central decision with its legal specific obligations as a natural path to optimize the knowledge of the product.

An holistic approach would recognise the obligations as part of an iterative development, not as a "blame" for the lack of initial data.

Recent criticisms were discussing the difficulty that Industry shows to follow the agreed specific obligations and HTA bodies[6] regretting to see suboptimal data collected post-initial CMA. On the other hand all CMA[7] granted since 2010 have been converted into full approvals and no penalties have been imposed due to compliance infringements, although delays have been reported in a minority of cancer drugs.

There is a need to recognise that evidence-generation is a continuum all along the life-cycle of product. In fact, data collected in clinical studies, within a homogeneous patient group selected according to specific common eligibility criteria, do not truly reflect the medical use in real-life setting. It is therefore necessary to place the product on the market as soon as a satisfactory efficacy and positive benefit/risk have been demonstrated, at least in one sub-group of patients and to collect real world data afterwards to bridge and refine the safety/efficacy evaluation, the effectiveness, as well as the best sequencing of the treatment. This will help defining the optimal practice of care.

The pharmacovigilance legislation and its new tools (i.e. Periodic Benefit-Risk Evaluation Report) are crystallising the need for a continuous benefit-risk assessment. The proposed adaptive pathway is also emphasizing this and CMA with its specific obligations should be viewed as an holistic process to gain knowledge on the product from research to its proper usage.

The CMA with its annual review is a sort of rolling review of data as they accumulate. A rolling process would support efficiently innovative and adaptive approach to allow time sensitive submission of studies as they are completed. This will enforce the vision of the continuum evidence of a life cycle product.

Conclusion

CMA is an important regulatory procedure to allow flexibility, innovation and adapt ways to early access to patient. The recognition of the positive value of the CMA by all stakeholders can be developed through:

- Proactive and pre-planned CMA request by industry;
- An accelerated CMA assessment enforced by an early dialogue with all stakeholders;
- Achieving appropriate levels of evidence at each milestone of decision-making and acknowledgement of uncertainty being inherent to the process of research and benefit/risk assessment;
- True integration of controlled clinical trial data with real world data evidence (usage of the product in real life) to bridge knowledge;
- Agreement that the product knowledge is a continuum of evidence and the first set of data is a starting point of an iterative decision-making for which the specific obligations is a natural path to the next set of data;
- Active management of uncertainty through iterative steps at each time point of decision-making (regulatory authorization, reimbursement, or treatment);
- Joint responsibility to collect the right data at the right moment to allow a responsible and flexible decision for all stakeholders.

It is time to seize innovative opportunities like CMA for the concrete added value they can bring, as exemplified by the first recent EMA[8] fast-track approval combining CMA with an accelerated assessment. This new case reflects the willingness and possibility to use CMA in a more positive way to "tag" innovation.

4 Boon et al. Clin Pharmacol Ther. 2010 Dec; 88(6):848-53. doi: 10.1038/clpt.2010.207. Epub 2010 Oct 20

5 A.H. Arnardottir et al. Additional safety risk to exceptionally approved drugs in Europe? Br. J. Clin. Pharmacol., 72 (3) (2011), pp. 490–499

6 EURORDIS Meeting 24 feb 2016

7 Banzi R, et al. Approvals of drugs with uncertain benefit–risk profiles in Europe. Eur J Intern Med 2015; 26: 572–584.

8 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/12/news_detail_002448.jsp&mid=WC0b01ac058004d5c1

Affordable and equal access to medicines: The EU has the mechanisms to do more

Biljana BORZAN
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Member of the of the ENVI committee

Insufficient access to medicines is a serious threat to the well-being of a large section of the population in Europe. The prices of many innovative medicines were too high even before the economic crisis, but the real extent of the problem became apparent when public budgets were cut.

Economic recovery is on course, but the problem will not go away. Quite the opposite, the growing need and rising costs of healthcare as a result of an ageing population will further intensify the situation.

Various factors influence the availability of medicines, such as the selection of medicines on the market, the focus of pharmaceutical research, supply systems, financing mechanisms, pricing, reimbursement and cost-containment policies of individual countries, as well as patenting rules.

As the factors are many, there is no single solution. The EU can definitely be a part of the solution, both directly and indirectly. The European parliament has discussed the situation at length at various levels, and the S&D group has put together a task force within the Committee on environment, public health and food safety to the work on this issue. The task force has come up with a set of recommendations for direct EU action which we hope will lead to concrete measures.

As the shadow rapporteur on the ill-fated transparency directive I would like to use this opportunity to call on the Commission to give it another go. The directive was meant to ensure the transparency of measures established by EU countries to control the pricing and reimbursement of medicinal products. It would have made the bargaining position of Member States stronger and resulted in lower prices.

The same can be said of a comprehensive joint procurement system between Member States. Such a system on an EU level is a long shot, but individual states are already doing it amongst themselves. I firmly believe that joint procurement is a long term solution to a part of the problem.

Furthermore, a comprehensive analysis should be made on the differences in prices of the same medicines in different member states, taking into consideration the difference in purchasing power. My guess is that the results would be very interesting, especially for a Union that is based on a Single Market.

When speaking of the Single market, the provisions of the directive 2001/83 on medicines for human use that regulate distribution and supply could be adjusted.

The EU should also act on the cross-border directive to develop a European framework which would provide reliable, timely, transparent and comparable information on the relative efficacy of health technologies to support Member States' decisions.

In discussions about prices and availability of medicines the discourse often goes the way where the pharmaceutical industry is portrayed as the enemy whose greed is the main obstacle to treatment. That is one of the reasons those discussions rarely lead to constructive solutions.

Pharmaceutical industry is a key partner and stakeholder in finding a way to provide affordable and innovative medicines to the needy. Without their involvement the whole idea is doomed to fail.

But they should be prepared to make concessions as well. We need transparency in the production costs of medicines. This is a condition to achieve the right balance between a fair price for patients and a fair return on investment for industry.

Furthermore, conditions such as affordable pricing and non-exclusive licencing should be put in place when a large share of research and development that went into a new medicine is publicly funded.

In its "Conclusions on the EU role in global health" from 2010, the Council stated that the EU should ensure that public investments in health research secure access to the knowledge and tools generated as a global public good and help generate socially essential medical products at affordable prices, to be used through rational use.

"Evergreening" of patents is a practice that has a negative impact on the affordability of medicines. It allows the patent holder to go around the patent legislation and keep the patent indefinitely. With this practice affordable generic medicines are unfairly prevented from reaching the market.

I believe that we should promote the competition between generic medicines and established medicines where the patent has expired. This can incentivise innovation and reduce pharmaceutical costs.

On the other hand, the EU should streamline the process of getting new medicines to the market and support the independence and transparency of EMA in the assessment and approval of medicines.

To conclude, we will never achieve the equality the EU treaties speak about if we have such inequalities in access to medicines as they exist today. Even within the existing system, where subsidiarity is the key word, the EU can play a very positive role in getting medicines to become cheaper and more available.

Access to Innovative Therapies: The Patients' Perspective

Nicola BEDLINGTON
Secretary General of EPF

The **European Patients' Forum (EPF)** is an umbrella organisation that works with patients' groups in public health and health advocacy across Europe. Our 65 members represent specific chronic disease groups at EU level or are national coalitions of patients. EPF reflects the voice of an estimated 150 million patients affected by various chronic diseases throughout Europe.

Innovation is the current buzzword in healthcare debates. However, a common and clear definition is still lacking. The European Patients' Forum (EPF) believes in patient-centred, valuable innovation. Too often the end beneficiaries, the patients, are not involved in the innovation process, whilst their meaningful involvement, from research to implementation is crucial to fulfil patients' unmet needs and improve research results.

A valuable, patient-centred innovation

How we currently determine what a valuable innovation is and how it is rewarded is a critical issue. EPF believes that valuable innovation cannot be defined without the involvement of patients in setting research priorities and that evaluation is needed to determine where innovation adds real value to patients. There is a need for a common definition, starting from patients' and societal needs, as well as for joint principles, considering that health is an investment, and a right.

At EPF we promote patients' involvement from the "idea" stage through to implementation and evaluation. Patients are part of the solution, they are the experts to identify therapeutic needs and point out inefficiencies and waste in systems and processes. There is strong evidence that patient's involvement leads to better quality research results. Moreover, the involvement of patients in the different research phases will consolidate the trust and acceptance of research outcomes by the patients and the broader public.

Healthcare for all

Access to healthcare is central to EPF's vision, one of the pillars we clustered our activities around. In our 2010 position paper on health inequalities, we indicated that patients with chronic conditions are even more vulnerable, due to their specific needs. More recently, our paper on discrimination[1] further highlights some of the crucial access issues faced by patients both in healthcare and in the areas of education and employment. We call for policies to tackle health inequalities that address both prevention and the needs of patients when managing their disease.

We will also shortly publish a position paper on "Defining and measuring access to healthcare: the patients' perspective", which will examine the key dimensions of "access" that matter to patients in order to encourage the development of more accurate indicators to assess patients' access to health and social care across Europe.

A new pricing system is needed

Innovative technologies, at least in the short-term, are often expensive. While they can result in important benefits for patients and thus contribute to overall societal objectives, at the same time they exert pressure on national budgets. A major challenge for European health policy is to address and attempt to reconcile the sometimes conflicting objectives of providing high-quality treatment, ensuring equity and solidarity, and containing costs.

1 http://www.eu-patient.eu/globalassets/policy/anti-discrimmination/epf-position-paper_equal-treatment-in-education-and-employment.pdf

Pricing and reimbursement decisions are currently taken without patients' participation, and criteria are not always transparent. Healthcare systems make decisions on which treatments and medicines to make available and under which conditions, very often without patients' involvement.

The system of pricing and reimbursement needs to be rethought and meaningful alternative strategies to pricing mechanisms should be investigated. External reference pricing methods deserve further examination while the scope of value-based pricing would definitely benefit from the involvement of patients.

We believe a fair, transparent and participatory system will contribute to better decision-making around pricing. To further stimulate debate at European level, EPF will publish a statement in the first half of 2016 outlining the core ethical principles and reflections from the patients' perspective on medicines pricing and reimbursement.

Riga Roadmap

In June 2015, under the auspices of the Latvian Presidency, a group of European health stakeholders from different horizons agreed on the Riga Roadmap[2], an action plan to make EU health systems sustainable, equitable and participatory. The document sets out key recommendations to prevent health inequalities by developing universally accessible health systems; make healthcare systems sustainable by investing in innovation; and ensure universal access to high quality and participatory people-centred health services.

The Roadmap has received very positive feedback from the EU institutions and seeing these recommendations transposed in real tangible policy measures would be fantastic.

Patient Access Partnership

EPF was a founder member of the Patient Access Partnership (PACT) and contributed to setting up the European Parliament Interest Group on Patient Access to Healthcare. Officially launched on the 27th of January 2015, this informal group aims at providing a platform for discussion and concrete actions to improve access of EU citizens.

The support the PACT has received from many MEPs demonstrates a strong and cross-party commitment to access to healthcare.

The group met twice in 2015. In June a meeting gathering key healthcare stakeholders discussed the opportunity to create synergies between the different EU agendas related to access to healthcare. The group also met in November to reflect on the opinion on access to healthcare drafted by the European Commission's Expert Panel on Effective Ways of Investing in Health.

The actions taken by EPF on the many dimensions of access to innovation and access to healthcare underline our strong belief: there is a need to identify effective and concrete actions at EU level to provide all patients across Europe access to high-quality, affordable treatment.

More information: www.eu-patient.eu - info@eu-patient.eu

2 http://www.eu-patient.eu/News/News/riga-roadmap-published--key-recommendations-for-patients-participation/

Enhancing health delivery model efficiencies to increase patient access to high quality care in Europe

Erik TYSSIER
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The new Juncker Commission has committed to "driving change and to leading an EU that is bigger and more ambitious on big things, and smaller and more modest on small things"[1] ; to do different things, so as to deliver results. It is clear that the time has come for Europe's health systems to move towards "different things" if we want to preserve universal access to health in Europe. For Europeans, universal health is not an aspiration – it is a basic human right, and all of us – citizens, industry, governments, payers, healthcare professionals – are confronted with a widening gap between what society expects, and what is achievable under the current rules of the game.

It is no secret that complex issues such as our ageing population, the increase of chronic diseases and the cost of innovation are challenging existing health models. Confronted by years of economic recession, European health systems are being required to be much more cost-effective, while preserving patient access to high quality healthcare services.

In a context of austerity, short-term efforts to drive budget healthcare sustainability have concentrated on cost-cutting of pharmaceutical spending across all segments of the pharmaceutical spectrum, threatening access of European citizens to high quality affordable medicines such as generics and biosimilars. However, if we aim to address stretched healthcare resources, sustainability and access issues, this situation simply won't solve the problem. The status quo is also no longer an option and it is indeed time to think how we can do things differently, acknowledging the current pressure, while increasing health delivery models efficiencies.

We must confront existing dogma, carefully examine what is not working and what could work better and collaboratively bring new ideas to the table. We must be ready to take different approaches, to identify and address inefficiencies that exist across the health delivery models serving patients, if we hope to preserve people's access to universal health.

The World Health Organisation has estimated that as much as 20 percent of health budgets is wasted due to various inefficiencies – in some cases, this is as high as 40 percent[2].

Europe simply cannot afford to waste resources of that scale.

It would be easy, of course, to argue that reforming Europe's healthcare systems is easier said than done. But what if solutions already existed? What if, with the right combination of willingness, and the right partners working together, the promise sought by so many patients could be achieved in much less time?

By enabling a much greater focus on the right medicines , to the right patients at the right time, the promise of sustainable, high quality and accessible health systems in Europe is achievable.

Talking about the right medicine, a perfect example of what could be more systematically addressed is the slow penetration of generics and biosimilars in Europe, particularly in some Member States. Here is a situation where the same health outcomes can be provided whilst enhancing access to treatment – with no compromise on quality, without turning the healthcare system upside down, but just through willpower, policy and co-operation.

As shown in a recent IMS study[3][i], between 2005 and 2015, twice as many patients have been treated across seven diseases areas, without any impact on treatment costs due to the use of generics. This shows the crucial role generic medicines play in increasing access to medicines for patients in need.

Drivers of generic and biosimilar penetration should be stimulated, especially in countries where penetration is slow and low, notably through:

- Better awareness of the benefits of generics and biosimilars by key stakeholders (prescribers, pharmacists, and patients);
- The set-up of the right incentivised schemes to enhance the usage of generics and biosimilars;
- Addressing pricing and reimbursement measures such as tendering, which tend to increase the risk for supply swings;

The Commission, the Member States and the pharmaceutical industry have - in the context of the European Semester process and national discussions on stability pacts - an opportunity to make a stand to deliver quickly on a better rational use of medicines, unlocking the potential that generics and biosimilars have to offer with regards to increased access and sustainable. In such context, all segments of the industry should be represented and considered when discussing measures to enhance predictability and the sustainability of the healthcare budgets.

Beyond better use of generics and biosimilars, the growing pressure on healthcare budgets is also exposing other gaps in our current health delivery models. We need to move from responding to sickness, towards planning for wellness, keeping people healthy, looking ahead and thinking in the widest sense about efficient care. We must look for new approaches to improve health outcomes, leveraging the benefits of technology, using patient, healthcare professional and payer insights to hopefully anticipate and meet their needs. If the majority of known treatments are delivering their promises to patients, we should also acknowledge that the one size fits all approach in some cases has reached its limits, leaving some patients with specific needs with no real answer.

Value added medicines can deliver on the promise of a more customized healthcare. Indeed and as recently highlighted by the Value Added Medicines group of Medicines for Europe[4][ii], value added medicines are medicines based on known molecules that address unmet healthcare needs and/or deliver relevant additional improvement for patients, healthcare professionals and/or payers through drug repositioning, drug reformulation, drug combination or new added service. Theses improvements should ultimately deliver additional health benefits for patients who need it and help to better manage their health conditions, reducing disease exacerbation and the need to move towards more cumbersome and expensive treatments.

Delivering better outcomes will run into a dead end if the pricing and reimbursement framework does not allow value added medicines additional benefits to patients, healthcare professionals and payers to be considered. Innovation needs to be rewarded.

We need a mind shift, a sea-change to improve the current way of assessing patient treatment solutions, in particular when providing new ways to use known molecules to improve outcomes. In an effort to reconcile innovation and universal access, clear pricing and reimbursement pathways should be opened to recognise the added value that optimized treatments can provide.

By enhancing the rational use of medicines, by gaining a better understanding of patients, healthcare professionals and payers needs and by leveraging innovation through the entire life cycle of a molecule, we can address more efficiently today's often costly, health delivery systems inefficiencies, in an effort to deliver better outcomes to the patients and the healthcare systems in general.

It is clear that it cannot be done alone, by any single player. We need big changes which will require the cooperation of everyone – from policymakers to patients, healthcare providers, payers and all segments of the pharmaceutical industry – taking into account all parts of the patient journey, if we want to preserve universal access to high quality care in Europe.

1 A New Start: European Commission work plan to deliver jobs, growth and investment - IP/14/2703
2 WHO, The world health report financing for universal coverage 2010
3 IMS (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective
4 www.medicinesforeurope.com

Pricing and transparency at the core of the EU policy on access to medicine

Gilles PARGNEAUX
MEP (S&D Group), Vice-chair of the ENVI committee

Today, insufficient access to essential medical products poses a serious threat to the well-being of a large section of the population in Europe. The EU, the WHO, the Charter of fundamental Rights all recognize the right of citizens to preventative healthcare and the right to benefit from medical treatment.

However various factors influence a proper access to medicines such as the selection of medicines on the market, the focus area of pharmaceutical research, pricing, etc. Pricing in particular, which is at the core of the issue of access to medicine, cannot be considered separately from the way we buy medicines. The H1N1 crisis has cast light on the EU's shortcomings as regards our common reaction to a European-wide sanitary crisis. Without any possible coordination, Member States bought vaccines on their own, with a dramatic result: an excessive number of vaccines were bought by some Member States and not enough by others.

The EU learnt from its mistakes. In 2013, I have been rapporteur on the decision on cross-border threats to health. One of the main achievements was the setting up of a legal basis for joint procurement of vaccines and medicinal products. Since the definition of this legal basis, access to vaccines in Europe is fairer, namely for the smaller Member States which cannot afford highly-priced medicines. Now, the EU is able to launch by itself the production of vaccines.

These joint procurements are an important step forward to deal with epidemics but also to negotiate lower price for medicine. To negotiate as the EU is way more effective than to negotiate alone with pharmaceutical companies. This is the very reason why the S&D group encourages these joint procurements: to strengthen our negotiating power driving down purchasing prices, thus providing lower costs for patients.

To foster this achievement, the decision on cross-border threats to health also designed the concept of «*European health emergency situation*" as well as strengthened the position of the European Commission as coordinator of Member States actions when it comes to face a sanitary crisis. A whole new design of the way we face health threats and respond to them, namely the purchasing of medicines and vaccines, brought about a new way of considering the access to medicines in Europe.

This action on pricing of medicine must go along with a strong policy on transparency from the industry. More information means better negotiations and fairer deals for the citizens. This is why as S&D group we call for a new transparency directive following the withdrawal of Directive 89/105/EEC, that aims to ensure the transparency of measures established by EU countries to control the pricing and reimbursement of medicinal products. This is only through transparency enhancement we will be able to go further in our fight for a better and fairer access to medicines.

From another point of view, transparency must also apply to the public access to data on all clinical trials carried out for new and existing medicines in Europe. The tragic death in Rennes, France, of a patient who attended a medical trial forces us to act. The European parliament, through the S&D group, held an oral question on the matter during the January plenary session, but more can be done. When accessing to medicine, consumers must have the most comprehensive information on drugs they are about to take. Right now, industries and even EMA are trying to water down the provisions of the Clinical Trials Regulation.

Pricing and transparency are two faces of one medal. They are the backbone of the action of the S&D group and of my personal actions when it comes to access to medicines. To conclude, this is the EU we are looking for: a protecting EU allowing a universal access to medicines and all the practical way to make it happens.

Transparency of Clinical Trials Data: opportunities and risks

Glenis WILLMOTT
MEP, (S&D Group)
Member of the of the ENVI committee

When I was named as the European Parliament's rapporteur on the Clinical Trials Regulation back in 2012, I quickly realised that we had a big problem with transparency. Thousands of clinical trials are authorised every year in Europe but only about half of all trial results are ever published. As well as some results not being published, there's a problem with publication bias as positive results are twice as likely to be shared, while those that are negative don't see the light of day. I worked hard to ensure that once the new legislation comes into force, this will no longer be possible.

Why? Firstly because if only half of trial results are published, it means we're only getting half the picture, and if only positive results are published, the overall picture will be biased. Anyone looking at the results, such as doctors or policy makers, may get an inaccurate impression of how effective a particular medicine is. This was the case with the flu medication Tamiflu: governments around the world spent millions stockpiling this medicine on the basis of published studies that suggested it would be effective in a flu pandemic. It later emerged that the drug's developer had withheld some research, and when this was finally published the analysis found that Tamiflu probably wasn't as effective as thought.

What's more, if some trial results are never published, trials may be repeated unnecessarily because no one knows about the earlier results. Not only is this unethical – carrying out unnecessary trials goes against all ethical principles – it can also be dangerous. For example, in 1980 a trial on the anti-arrhythmic drug Lorcainide found that more people died among those taking the drug than among those taking a placebo. The results of the trial weren't published until 1993 and in the meantime doctors, unaware of this study, continued to prescribe similar anti-arrhythmic medication; it's estimated that in the US alone 100,000 people may have died unnecessarily because doctors and researchers weren't aware of this risk.

The recent tragic events in France, where one subject died and several others were severely brain damaged during a phase I trial, only serve to demonstrate why transparency is so important. Events like this are extremely rare but when they do occur, researchers need to know what happened to inform future research and avoid the same mistakes being repeated; making sure this information is available to everyone is good for science as a whole.

There's also a strong moral argument for greater transparency. When people volunteer to take part in a trial, they do so in order to help scientific research and humanity as a whole. As regulators, we have responsibility to ensure that these expectations are met and that the results of trials are never simply hidden away but go towards supporting our collective knowledge for the good of everyone.

As for the risks of increased transparency? When we were working on the new legislation, it was argued that the new rules would drive research out of Europe, as companies wouldn't want information on new drugs available to competitors. But the legislation is clear that trial results and methodology should be published, not commercially sensitive information. Indeed, some pharmaceutical companies have already started to publish this information voluntarily. In fact, greater transparency should be a good thing for the industry, as researchers won't invest time and money in something that someone else has already found to be unsuccessful.

When the new legislation comes into force, the results of all clinical trials in Europe will be published. Under the Clinical Trials Regulation, a summary of trial results must be published a year after the end of the trial and the full clinical study report will be published once a medicine receives marketing authorisation. This means that all trial results will be available to everyone – whether that's doctors or patients who want more information on a particular medicine, or researchers who can use the results to inform future work.

The EU now has the strongest clinical trial transparency requirements in the world and I believe this is something we should be extremely proud of. I hope this will set a precedent, for both other EU legislation (for example on medical devices) and for the rest of the world.

The real risk is in science being hidden away. Patients shouldn't be put through unnecessary, and sometimes dangerous trials, if we already know a drug won't be effective. And people who are making decisions about the effectiveness of a particular medicine shouldn't have to hunt for the information they need, only to find it isn't available. The history of science is based on people building on the work of others but to for this to continue we must be able to see the results of other people's work, and how they got those results. In this way, greater transparency in clinical trials is good for industry, good for patients and good for science.

It's the data, stupid!

Thomas ALLVIN
Director Healthcare Systems
EFPIA

- How Real World Data and tracking patients' health outcomes can revolutionize pharmaceutical development and healthcare systems

> *There are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns – the ones we don't know we don't know.* – Donald Rumsfeld

For several decades, the clinical trial has been the gold standard of measuring the safety and efficacy, and indirectly value, of pharmaceuticals. The basic principles for conducting clinical trials were developed in parallel with the ascent of modern medicine, and during the latter half of the 20th century the rulebook for conducting trials grew thicker and more complex. Regulatory agencies is both the EU and the US demanded more and more documentation demonstrating the performance of new drugs, from the relatively small scale phase 1 trials testing the safety profile of new molecules to the large phase 3, randomized controlled trials (RCT), often encompassing thousands of patients.

With the results from the Clinical Trials, truckloads full of data, the pharmaceutical company could apply for marketing authorization, and then for a decision on pricing and reimbursement (the latter often requiring more studies proving cost-effectiveness, added therapeutic benefit or socio-economic value).

For many decades, all these studies – conducted before the marketing of pharmaceuticals – represented the great known known of medical science. No other item of healthcare expenditure has been so thoroughly assessed when it comes to effect and performance as pharmaceutical products.

But does clinical trials provide the full picture? Is it really a known known?

Clinical trials are, by nature and regulation, conducted in controlled circumstances. Patients are recruited according to certain procedures, the experimental drug is administered according to strict protocols et.c. But real clinical practice - the reality facing millions of patients and healthcare professionals every day in hospitals and primary care centers - is not so well structured. Not every diagnosis is correct. Clinical protocols are not always followed, sometimes for good reason. Not all drugs prescribed to patients are taken by the patient according to the prescription. Some patients have more than one disease, or take more than one medicine, which can impact the final outcome. The reality of treating and curing patients is much more complex and "messy" than the orderly world of clinical trials.

Most healthcare professionals know this. This is the known unknown of clinical practice. We know that some pharmaceuticals can behave differently when meeting real patients in real healthcare settings, but in what way? In most cases – shockingly enough – we just don't know. For most pharmaceuticals marketed according to the traditional model, the structured collection of data stops as soon as they are introduced in the healthcare system. There are systems for detecting adverse events – serious side effects – but not for discovering if a drug is a little less or a little more effective than previously known. That is worth thinking about, considering how much money is spent on different treatments. And if our knowledge is a bit fuzzy about the exact effect of pharmaceuticals used to treat patients, it is severely lacking for other parts of healthcare expenditure – sometimes completely non-existent. Most other innovations in healthcare are introduced based on much less evidence than the average pharmaceutical product.

So what to do? Undoubtedly clinical trials continue to have an important role to play, but the solution lies in combining clinical trial data with what is commonly known as real world data (RWD). Real World Data is all health data that is generated and collected in real clinical practice, in hospitals and clinics all across the healthcare system, and also in the administrative files of payers and insurance companies, and sometimes also in patient's homes. Sometimes RWD is collected in a structured way for a specific purpose, for example when a pharmaceutical has a conditional marketing approval and the regulator requires additional studies, or when healthcare professionals collect data to, for instance, compare the effect of different surgical procedures or measure the spread of resistant bacteria.

But most RWD is scattered across the healthcare system without any possibility to bring the data together. They are noted down in individual patient's records, recorded in registries kept by small groups of specialists for tracking a specific disease in a selected number of patients, or collected for reimbursement purposes and then discarded. Considerable efforts are now being made both by public and private stakeholders to unearth and utilize all this information for new purposes.

For pharmaceutical development, Real World Data has become more and more important due to scientific progress. With the progress in genomics, and the possibility to tailor make drugs for patients with a specific genetic makeup, and also progress in developing pharmaceuticals for rare diseases, medicine has become more and more personalized, affecting small groups of patients. That makes it difficult, sometimes impossible, to recruit patients for the traditional phase 3 clinical trials. Instead, new models are needed, where innovative medicines are introduced for a limited number of patients in areas of unmet medical need, based on earlier phase trials, and then systematically followed up in clinical practice and successively introduced to new groups of patients. This model, often

called adaptive pathways, will mean that more information is collected on the actual effect of a pharmaceutical during the entire life cycle of a drug than under the traditional model. As information on the effects of the drug is continuously collected and analyzed, earlier decisions on clinical guidelines, cost-effectiveness, pricing and reimbursement, might have to be re-assessed and adjusted. We will start mapping out the known unknown territory, creating real knowledge of the effect and value of pharmaceuticals in clinical practice.

The other driver of Real World Data in healthcare is the digital revolution. As Electronic Health Records start replacing patient records written on paper, disease registries become digitized, hospitals introduces electronic decision support systems and patients are starting to collect their own health data using all the new wearable's and apps coming into the market, the possibility to actually harvest all this data and put it to good use appears at the horizon. At the horizon, but not in the bag just yet. Several barriers must be overcome, and sometimes investments made, for healthcare systems and all stakeholders to be able to reap all the benefits of the real world data revolution. Data are not always generated according to the same standards, and is therefore not comparable. E-health systems are not always compatible between hospitals or countries, and many patients still do not have a single, electronic health record with all their health data collected in one place. Data collected for different purposes can often not be linked together, even when they relate to the same patient. Regulation sometimes stops data from being transferred between systems and used for research or quality improvement.

But these investments need to be made, and the barriers overcome. Because the potential gains for patients and healthcare systems goes far beyond the effectiveness and value of pharmaceuticals. It concerns the entire healthcare system, and every single euro spent on health and wellbeing. When our healthcare systems are measured, assessed and compared today, we mostly see what is easy to measure – number of hospital beds, number of doctors, number of screenings for cancer, numbers of hospital readmissions for diabetes, and on and on. The capacity to collect and analyze real world data will make it possible to measure actual health outcomes for patients, not only crude measures such as mortality and healthy life years, but granular information about quality of care and the quality of life after different types of healthcare interventions. With more information about how different interventions actually compare in terms of health outcomes for patients, healthcare managers and policymakers will be able to take much more informed decisions on implementing clinical practice and resource allocation, creating not only better health outcomes for patients but also getting more value from every euro spent on healthcare. In an era of ageing populations, when healthcare budgets and social security systems are put under increasing pressure, this is a reform that European healthcare systems cannot afford to do without.

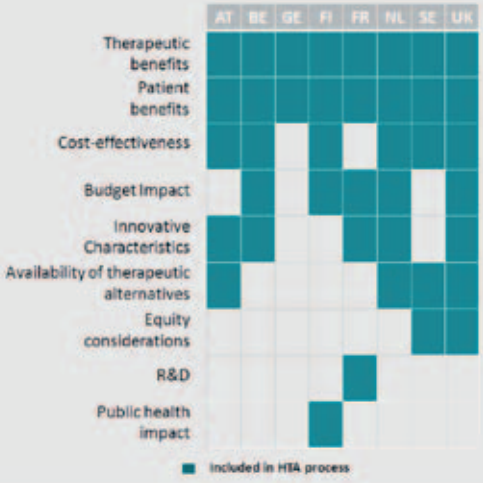
But beyond this horizon lies the next revolution, when we have enough data and the different data sources are connected and compatible enough for the use of big data analytics and machine learning methods for discovering patterns and connections we didn't even look for. That means venturing into the unknown unknown, and finding answers to questions we hadn't thought of asking. This could bring about a completely new model for discovering innovations, from products to treatment pathways, and for identifying waste and inefficiencies in the system. What the potential gains for human health could be once we have these tools at our disposal, is something we today can only speculate about.

pharmaceutical expenditure

Throughout Europe medicines are only reimbursed if value can be comprehensively proven across multiple dimensions

Countries with formal HTA systems in place*

Reimbursement criteria across countries†



Sources: * EFPIA. Role and Impact of Health Technology Assessment (2011); † Sorenson et al. Ensuring value for money in health care (2009)

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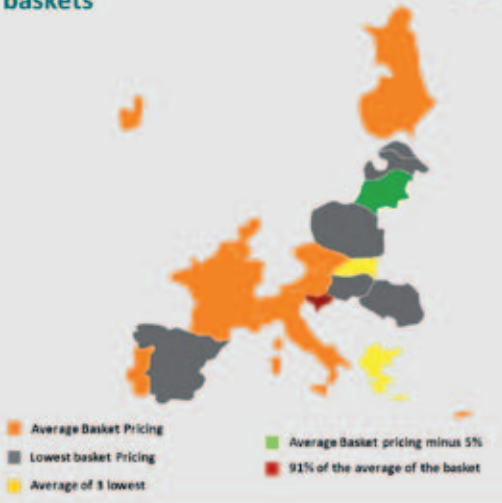
need for differential pricing in Europe

External reference pricing is widely used to establish and regulate Medicines prices in Europe

Usage of External Reference Pricing (23 out of 27 EU Member States)

Variations in constructions of pricing baskets



Sources: Leopold, C. et al. Differences in external price referencing in Europe (2012).

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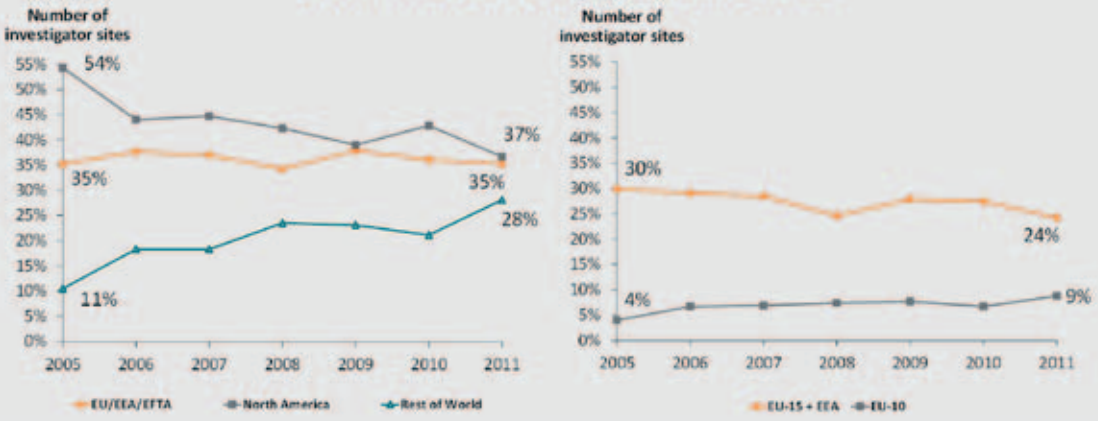
resiliency to the crisis

Europe has maintained its share of clinical trials notably due to positive developments in Eastern Europe

Investigator sites for clinical trials (2005-2011)

Number of investigator sites involved in pivotal clinical trials submitted in Marketing Authorisation Applications to the Agency per region and year



Note: EU-15 includes the member states of the European Union prior to the accession of the ten new countries on 1 May 2004, plus EEA countries.
EU-10 includes the 2004 accession countries.
Source: EMA 2013

efpia

resiliency to the crisis

The pharmaceutical industry is emerging from its "R&D productivity crisis" with significant innovations

Number of New Therapy Drugs approved and Sales (2004-2014)

Source: Author, M. (2015). 2014 FDA drug approvals. Nature reviews drug discovery, 14, pp. 77-81.

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Healthcare payers: priorities for long-term sustainable access to innovative pharmaceuticals

Dr. CHRISTINE DAWSON

Director ESIP, Coordinator – Medicines Evaluation (MEDEV) Committee

Recent concerns regarding the very high prices demanded for some innovative medicines have highlighted the need for an EU-wide reflection on this issue. Indeed, the introduction of new medicines presents serious challenges for the pharmaceutical sector, public health, health equality and the sustainability of healthcare systems. These four dimensions need to be taken into account when reflecting on a European strategy in the pharmaceutical area. Areas of conflict between them need to be carefully addressed in order to find the right balance between incentives for innovation, necessary to provide patients with high quality medicines, and the promotion of universal access to healthcare, where highly constrained health systems need to make efficiency gains to ensure financial sustainability and equal access for all.

In their recent position paper published in October 2015[1], ESIP and AIM[2] identified a number of priority areas for action to improve access to innovative medicines in the context of sustainable health systems.

Steering pharmaceuticals R&D on the basis of needs

Investment in research and development (R&D) of pharmaceuticals is a precondition for the availability on the market of new technologies likely to save lives or improve health. To maximize the benefits for patients and ensure access to innovative medicines within sustainable health systems, public and private investment in R&D should be steered towards public health needs such as those identified in the WHO priority medicines for Europe and the world report 2013[3]. Aligning research priorities of the industry with those identified by public authorities may reduce the uncertainty for the industry and accelerate access to valued medicines. Public funding should be accompanied by conditions for delivery and use of the results e.g. access to data, open licensing; and public involvement in R&D costs of commercialised medicines must be transparent and reflected in their final price. In addition, different models for financing independent research carried out in the public interest should be explored, e.g. taxing the marketing expenditures of industry, as exemplified by the programme on independent research on pharmaceuticals set up by the Italian Medicines Agency (AIFA)[4].

Ensuring a central role for health technology assessment (HTA)

The development and use of transparent HTA tools and processes should be promoted at national and EU level to support Member States in their evidence-based pricing and reimbursement decisions. At EU level, cooperation on HTA through the HTA network and EUnetHTA can benefit both Member States and society by building capacity together. To realise these benefits, complete transparency is necessary between HTA bodies as well as towards other stakeholders and the public to

1 http://www.esip.eu/files/ESIP-AIM%20Joint%20position%20on%20access%20to%20innovative%20medicines.pdf

2 International Association of mutual benefit societies

3 http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf?ua=1

4 http://www.agenziafarmaco.gov.it/wscs_render_attachment_by_id/tipo_file0109.pdf?id=111.109018.1188484620191&language=IT&lenient=false/

achieve acceptance and trust. Trust in high quality HTA reports is a central precondition for a widespread national uptake and reuse of joint assessments in Europe. Full transparency will also facilitate joint evidence generation and the sharing of expertise and information with countries with limited resources and where available data on a new technology is limited; it is also a precondition for the comparability of data across Europe and the transferability of the results at national level. In this context, efforts by EUnetHTA to develop web-based tools for sharing information and enabling additional data collection over the short and long-term (life data) e.g. by means of joint registries, is welcomed.

Strengthening national pricing and reimbursement mechanisms in an EU context

To address the challenge of spiraling prices of new medicines Europe's healthcare systems need to reflect on new, fair and affordable pricing and reimbursement models rewarding innovation that can prove added value for patients, providing equitable access across Europe and ensuring the long-term sustainability of healthcare systems.

Reimbursing products which do not provide measurable benefits for patients is unfair to society. Pricing and reimbursement procedures therefore need to set "evidence-based medicine" criteria (e.g. demonstration of the added therapeutic and/or economic benefit of the product compared to existing therapies, as determined by HTA). When added value is proven, fair and affordable pricing is essential. This requires greater transparency from industry and greater transparency and cooperation between Member States. Voluntary cooperation and tools for joint negotiations and joint procurement by groups of Members States are being explored, as exemplified by the recent agreement between The Netherlands, Belgium and Luxembourg.

Fora for exchange of information between competent authorities for pricing and reimbursement (CAPR) and between these authorities and stakeholders (under the process of Corporate Responsibility in the field of Pharmaceuticals) facilitated by the European Commission have in the past provided a safe harbour for discussions and exchanges in this field. They have led to the piloting of potential new approaches to specific pricing and reimbursement issues such as the method of coordinated access to orphan medicinal products (MoCA). We encourage the European Commission to continue to support these exchanges with the engagement of all relevant stakeholders.

Other measures

Finally, access to innovation needs to be balanced by supporting measures aimed at ensuring the sustainability of healthcare systems and patients' access to medicines. These include amongst others, promoting the uptake of generic and biosimilar medicines and monitoring and controlling anti-competitive behavior.

About the *European Social Insurance Platform* (ESIP)

ESIP represents a strategic alliance of over 40 national statutory social security organisations in 15 EU Member States and Switzerland. ESIP's mission is to preserve high profile social security for Europe, to reinforce solidarity based social insurance systems, and to maintain European social protection quality.

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Medicines for Europe: Better Access, Better Health

Jacek GLINKA
Medicines for Europe President

For most European citizens, access to healthcare and medicines is of fundamental importance to maintain a strong social fabric. Our industry shares this view and has consequently changed its name from EGA (European Generic and Biosimilar medicines Association) to Medicines for Europe: better access, better health. Our new approach is synonymous with renewed focus on delivering better access to high quality medicines for all European patients. We see better access to healthcare as an opportunity to improve the health of the population and reduce inequalities in Europe.

Generic medicines have delivered access for patients

In many ways, Europeans are blessed with healthcare systems that are helping them live longer, healthier and more fulfilling lives. Better access to medicines and improvements in care have significantly increased life expectancy across Europe. Our industry is proud to have played a big role in this development. When the EGA was established in 1993, generic medicines represented a fraction of Europe's medicine supply. 23 years later, our industry has not only become the largest supplier of medicines in Europe (56% in volume), it has also increased the access to key first line therapies such as hypertension or diabetes by a massive 100% over the last 10 years alone. All of this has been achieved without increasing the overall costs of medicines. Without generic medicines, Europeans would have to pay a staggering €100 billion per year on top of the current medicines bill to deliver the kind of access that we enjoy today.

The growth and expansion of generic medicines will continue to play an important role for the next few years as patents expire creating new opportunities for competition in pharmaceutical markets across Europe. While this is certainly positive, we also need to recognise how this fundamentally changes pharmaceutical policy. Europe is a continent of over 500 million people with growing healthcare needs which translate, for example, into 80 million patients relying on (mainly generic) hypertension medicine every day. Similarly, 30 million Europeans rely on (primarily generic) diabetes medicines every day.

Pharmaceutical manufacturing is important for medicines supply

Medicines for Europe recognises the tremendous responsibility in ensuring a stable supply of medicines for patients. This requires a more focused pharmaceutical policy that takes much greater account of manufacturing sustainability. The first element is to ensure that Europe's pharmaceutical industry is capable of supplying patients with the medicine they depend on. This requires a robust and efficient regulatory system to guarantee the safety, quality and efficacy of all medicines which can only be achieved through effective dialogue and cooperation between regulators, the industry and other stakeholders. With improvements in IT technology and more effective IT systems between the industry and regulators, we have a real opportunity to make Europe's regulatory system more efficient by focusing on the real patient needs and reducing administrative redundancies that waste time and resources for both regulators and industry. Moreover, thanks to its global leadership position in both regulation and manufacturing, Europe can take a leading role in promoting regulatory cooperation to improve marketing authorisation procedures, to manage global supply chains and to promote high EU-like global quality standards. The European Commission and the EMA – European Medicines Agency have already demonstrated the capacity to lead in this space in the context of the TTIP negotiations with the US, building on the concept of global development of biosimilar and value-added medicines.

Moreover, pricing and reimbursement policies need to promptly stimulate competition when pharmaceutical patents expire while at the same time encouraging the industry to invest in maintaining the production of essential medicines even when price competition is fierce. Treating medicines like a simple commodity is a recipe for trouble. Therefore our industry is reaching out to EU governments to negotiate stability pacts to create competitive and predictable markets for patients and healthcare providers as well as the pharmaceutical industry. Additionally, policy-makers need to stimulate more medicine manufacturing in Europe to avoid over-reliance on foreign suppliers. The recent Commission proposal to allow a "manufacturing waiver" under the Supplementary Protection Certificate (SPC) period is definitely a big step in the right direction to create manufacturing and employment opportunities for Europe.

More competition is needed in specialty pharmaceuticals

The high cost of new medicines has many healthcare policy-makers and advocacy groups concerned. Medicines for Europe is already addressing this concern by investing heavily (up to 17% of turnover into R&D) in biosimilar and value added medicines which bring competition to biopharmaceuticals, to specialty medicines and to pharmaceutical innovation. This is not only a development opportunity for our industry, it is also an opportunity for Europe to re-establish its leadership in pharmaceuticals through an accessible innovation policy.

Biosimilar medicines: A European success story

Technological advances and innovation have had a massive impact on the pharmaceutical industry, including the development of new and highly innovative biological medicines – a medicine whose active substance is produced by or extracted from a biological source. We have responded to this opportunity

with biosimilar medicines – medicines that are highly similar to existing biological medicines, without any clinically meaningful difference in terms of efficacy. **With more than 10 years of positive patient treatment experience in the market,** the use of biosimilar medicines will massively increase access to biological treatments. For example, access to filgrastim, which is used for neutropenia in chemotherapy patients, has increased by 44% thanks to biosimilar medicines competition. However, to achieve these gains in access, Medicines for Europe understands the necessity of engaging with patients, healthcare professionals and governments to share the understanding and the benefits that these medicines provide as was pursued under the leadership of the European Commission Consensus Paper on Biosimilar Medicines. Actually, biosimilar medicines show that Europe can make a real difference, for patients by increasing access, for quality by creating the global high standard for biosimilar medicines approvals, for value but promoting a stakeholder benefits model for market uptake, for sustainability by supporting a technological leadership position in the research, development and manufacturing of these medicines and for partnership by encouraging stakeholders to work together to improve access to medicines.

Competing models of innovation

For most policy-makers, the pharmaceutical industry is a binary world of "innovators" developing new chemical entities and "generic companies" bringing competition at patent expiry and this is reflected in the binary structure of most pharmaceutical pricing and reimbursement systems in Europe with one (high) price for new drugs and a heavily discounted price for generic medicines. This binary world view prevents our innovative industry from challenging the dominant, and expensive, pharmaceutical innovation model in two ways.

First, it limits the possibilities for our industry to develop competitive pharmaceuticals at patent expiry for more complex products with value added component in comparison with the initial originator product, because the economics do not always work under a generic reference price system. This explains the huge potential in the respiratory therapies like asthma or COPD and the new technology opportunities to apply for improved products with known molecules. In a similar vein, our industry is restricted in its ability to compete in innovation with the dominant model limiting our capacity to improve on drug delivery for better health outcomes or even to address unmet needs through, for example, drug repurposing.

For this reason, we have expanded our industry into **value added medicines aimed at optimizing, rethinking and reinventing existing medicines based on known molecules**, addressing unmet healthcare needs of patients through improved care delivery systems. Value added medicines are based on known molecules that address unmet healthcare needs and/or deliver relevant additional improvement for patients, healthcare professionals and/or payers. Relevant benefits include improved efficacy, safety and tolerability profile, better adherence, better quality of life, better convenience of use and/or patient preference. As a novel contribution to the prevention of therapeutic escalation, the rational use of medicines and improving equity, value added medicines will play a key role in improving the efficiency of Europe's healthcare systems.

Better access for a better health across Europe

Generic medicines, and increasingly biosimilar and value added medicines, are fundamental to the **sustainability** of healthcare systems: allowing healthcare providers to care for an ageing population, respond to increased incidences of chronic diseases, and manage budgetary constraints compounded by the high cost of new branded medicines. Thanks to competition from our members, the access of patients to high-quality medicines has doubled over the last ten years with no impact on treatment costs. By driving efficiencies and reducing avoidable costs for healthcare systems through improved medical adherence and better patient outcomes, generic, biosimilar and value added medicines are an opportunity for an efficient, access-driven healthcare system. To be successful in achieving this, our industry also needs to operate in an environment that stimulates competition at patent expiry including through increased cooperation with healthcare stakeholders.

With our deep expertise and knowledge and our ability to deliver positive change for healthcare, we are committed to working in **partnership** with all the healthcare community and policy makers to create **better access and better health for all European patients**. Our association is actively engaged in stakeholder and regulatory dialogues – providing objective and accurate information to help improve access to high quality medicines and create a more stable and competitive pharmaceutical markets in Europe.

Medicines for Europe remains engaged and committed to building on the relationships established over the last 22 years as the EGA. We will continue to be a trusted source of high quality information about generic, biosimilar and value added medicines as well as a passionate advocate of better access to better health for Europe.

We look forward to the next opportunity to provide you with further information about **Medicines for Europe**, its engagement and its strong commitment to deliver access to high quality medicines for all European patients.

About Medicines for Europe

Medicines for Europe (formerly EGA) represents the pharmaceutical companies supplying the largest share of medicines across Europe and is the voice of the generic, biosimilar and value added medicines industries. As a leading partner for better healthcare, we aim to increase the health and wellbeing of all Europeans through better access to high quality medicines. 80% of therapy areas are covered by the portfolios of the members of Medicines for Europe, thereby safeguarding the sustainability of Europe's healthcare systems for future generations. The vision of Medicines for Europe is to provide sustainable access to high quality medicines for all patients, based on 5 important pillars: patients, quality, value, sustainability and partnership. For more information please follow us at www.medicinesforeurope.com and on Twitter @medicinesforEU.

Ideas for a sustainable access to medicines in the European Union

Ismail ERTUG
MEP (S&D Group),
Member of the ENVI committee

The case of the Hepatitis pill "Sovaldi" which was placed on the market for 700 Euros a pill made the news in 2014 and drew broad attention to the problem complex of affordability, pricing and more general: sustainable access to medicines. It was a catalyst to the debate that was ongoing for quite some time and, of course, also my political group took up the debate establishing a task force "access to medicines". Inequalities in access have been existing in the past, but became more obvious and severe during the economic crisis. Across the European Union we currently are facing rising cost of treatment while health budgets are decreasing.

Ensuring equal access to medicines and healthcare is the core idea as everyone should have the right to receive good care, effective and suitable medicine in due time, quality and affordable price. This touches on several pillars of healthcare systems (pricing, transparency, reimbursement, research and development...) and involves many different parties (payers, insurers, pharmaceutical and medical companies of all sizes, health personnel, patients, decision makers). Debates in S&D's task force tried to take into account their different backgrounds and identified several options for action.

Pricing and transparency are playing a major role here. It is important to understand how prices are created, i.e. what share of R&D-cost is involved and how much public was granted, what is the added value of the medicine and how do we measure it. This demands more transparency from the industry side, but is supposed to reach a balance between patients' and payers' demand for a fair price and industry's expectations of a fair return on investment. More transparency is also needed to examine and compare prices (adjusted to purchase power parity) in the member states, enabling them to better negotiate prices. Joint procurement by member states may also be an option to obtain better prices and lower costs for patients.

But it is not only about focussing on prices and lowering cost. Achieving better treatment also involves strong research and development - be it fundamental research opening doors for new treatment or research done by companies to bring drugs to the market. Public funding for research and innovation for the development of new medicines should be strengthened. In this context we have to think about conditional public funding including inter alia affordable pricing or non-exclusive licencing.

Intellectual property - or, the way it is dealt with - is setting incentives for innovation and can be used as a tool to steer R&D-investment to areas where the market is not as profitable.

Changing patenting rules when large shares of taxpayers' money are involved and considerable profit can be expected as well as claiming co-ownership of intellectual property could prove as suitable means.

Apart from changing existing rules or establishing new regulations a less invasive option to improve access to medicines is a better exchange of good practises among member states. In general this concerns sharing information among member states on pricing, reimbursement, procurement policies, rational and safe use of medicines or structures of the healthcare system. Cooperation through health technology assessment networks can contribute to identifying safest and most effective treatments. From a technological point of view promoting eHealth and mHealth solutions ensures wider and more cost-effective access to care - always keeping in mind the need to ensure data protection and patient safety.Moreover, we must not forget to invest in educational programmes to strengthen health literacy and raise awareness of the responsible use of medicines.

Together with the European Social Insurance Platform (ESIP) and the Association Internationale des Mutualités (AIM) we had a successful conference in the European Parliament on the challenges of providing sustainable access to medicines. An audience of more than 150 participants from all relevant groups of stakeholders and decision makers proves strong interest in the issue and how important it is to move forward in the debates.

Ensuring fair and equal access to medicines is a complex task with many parameters and variables. There will not be the one comprehensive solution that fits all, but there are options for policies to improve every health care system where and when needed. Yet, the most important decisions are still left to the national level. However, Europe can put emphasis on important issues like research, shape the framework for intellectual property and patents or strengthen the exchange between stakeholders and decision makers. The Juncker-Commission has made "better regulation" their mantra, but unfortunately in the field of health politics any innovative regulation is missing. The strong interest in the topic shown by stakeholders, players and decision makers should make the European Commission change its mind - and let them provide proposals for ensuring sustainable access to medicines in Europe.

Be innovative think beyond boarder – cross border health care

Karin KADENBACH
MEP (S&D Group)
Member of the ENVI committee

After years of facing improvement the economic crisis caused a worsening in patient access. In 2013 18 million people in the European Union experienced a failure to fulfil their health care needs. Whereas in contrast, in the years before the number dropped to 15 million people. (EXPH; 2015)

Nevertheless, an Eurobarometer survey from 2014 detected that only five per cent of the respondents used the medical service in another EU country. But one third are willing to use another EU countries health system and additional 16 per cent stated that it depends on the country and treatment in general. Interestingly most of the respondents are aware of the possibility using an other countries health care system but did not have any detailed knowledge about the types of healthcare they could be reimbursed or that there could be a prior authorisation needed.

In general the Directive 2011/24/EU provides regulations on the EU level in the case of cross-border healthcare. This directive focuses on three main areas, namely rules regarding the reimbursement of costs in cross-border healthcare, responsibilities of member states and the cooperation between healthcare systems.

In the directive two potential ways of cross-border health care are mentioned: Chapter II and III refer to the individual movement of patients to another country in order to receive health care whereas Chapter IV refers to managed mobility. The first one causes a lot of uncertainty for governments because no one can predict the number of individuals claiming reimbursement for healthcare services abroad. In Chapter IV countries or regions could a priori agree on the conditions and the patient flow, whereby rules are more predictable for the patients as well as for the health care system. Moreover, health care professionals can either for patient care , a joint training or educations programs cross borders. Additionally services could also be exchanged or transferred without patients or provider moving. This includes the transfer of information, expert knowledge, laboratory services or protocol sharing.

Patients profit from cross-border collaboration by having an increased choice that results inreduced waiting time and proximity to care. Looking at the provider side, one can find an improvement in efficiency and quality. Additionally, also small institutions benefit from collaboration across borders. An increase of potential patients is leading to a greater scope of specialities (see Glinos et al.; 2015)

The MOT Report (Mission opérationnelle transfrontalière; 2015) found four main obstacles for well working cross-border cooperation. First of all healthcare is organised and planned on a member state level, thereby potential benefits of cross-border pooling of resources are hardly ever taken into consideration. For instance border town cooperation for emergencies would lead to faster and more efficient patient care. One should keep in mind that due to geographical and language barriers for the patient as well as for the health care provider consider treatment in another hospital constitutes an effort. Especially in the case of rare diseases patient in smaller countries often face difficulties to receive appropriate treatment. Last but not least also complex administrative procedures for patients as well as for healthcare personal are an obstacle for a cross-border cooperation.

So far there are only a few projects. Nevertheless important first guidelines for future cooperation are provided. The next step will be to identify best practices. This attemp will help to foster cross-border collaboration which would represent an improvement.

Looking at seven collaborations of hospitals in border regions Glinos and Wilmar (2015 35) found that the European Union found surprisingly little inclusion in the cooperation. Most of the projects stated on the base of local initiatives between the partners.

Glinos and Wilmar (2015 35) detected that the European Union are only to a minority involved to seven collaborations of hospitals in border regions.

Considering things already stated one can easily observe that some major steps are already taken to ensure patient access in cross-border health care. Nevertheless there is still a long way to go.

The European Union created with the Directive 2011/24/EU already the legal framework. It has to be observed why there is so little cooperation at the moment and how the application can be simplified. Nevertheless also actions from the member states are needed to build up cooperations between the border hospitals and to attract especially patients from rural areas.

Although I was the former health minister of Lower-Austria, I had sometimes found it difficult to find the right doctor, treatment and information.

When I was health minister in Lower-Austria, I tried to better communicate. I sometimes saw that we spent a lot of money on topics, on communication that didn't reach the people that really should be reached.

It makes no sense to produce a lot of brochures or to have a lot of material in a hospital and though we say literacy, this is not just about letters, but also pictures and pictograms.

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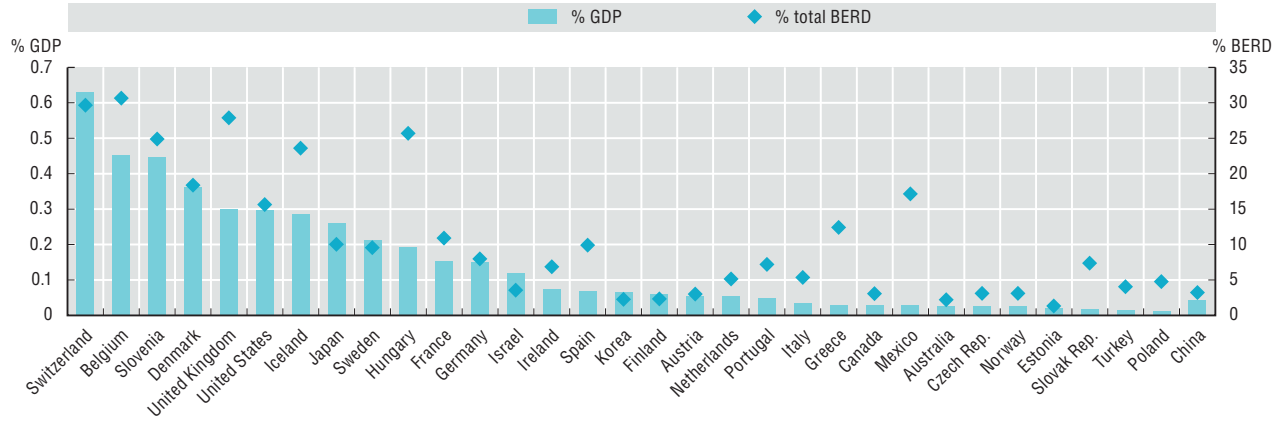
Special Eurobarometer 425: Patients' rights in cross-border healthcare in the European Union; Conducted by TNS Opinion & Social at the request of the European Commission, Directorate-General for Health and Consumers (SANCO)

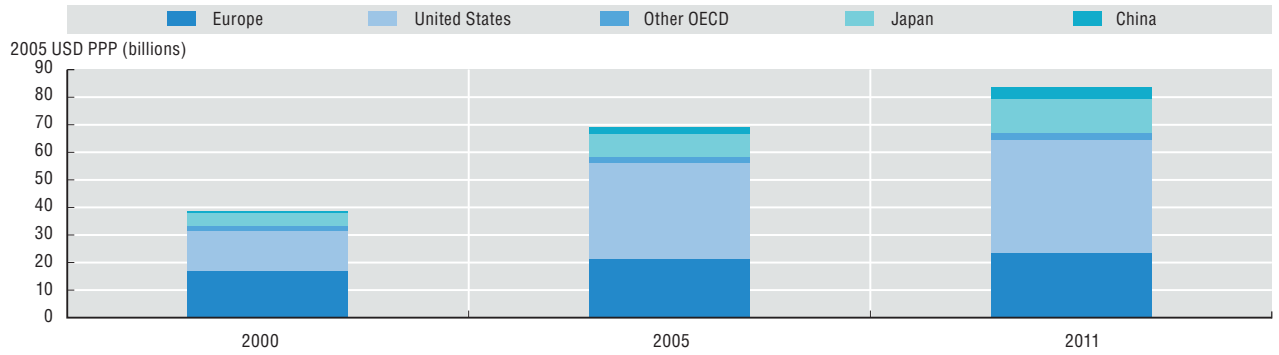
10.14. Business expenditure on R&D (BERD) in pharmaceutical industry as a proportion of GDP and of total BERD, 2011 (or nearest year)



Source: OECD Main Science and Technology Indicators Database.

StatLink http://dx.doi.org/10.1787/888933281362

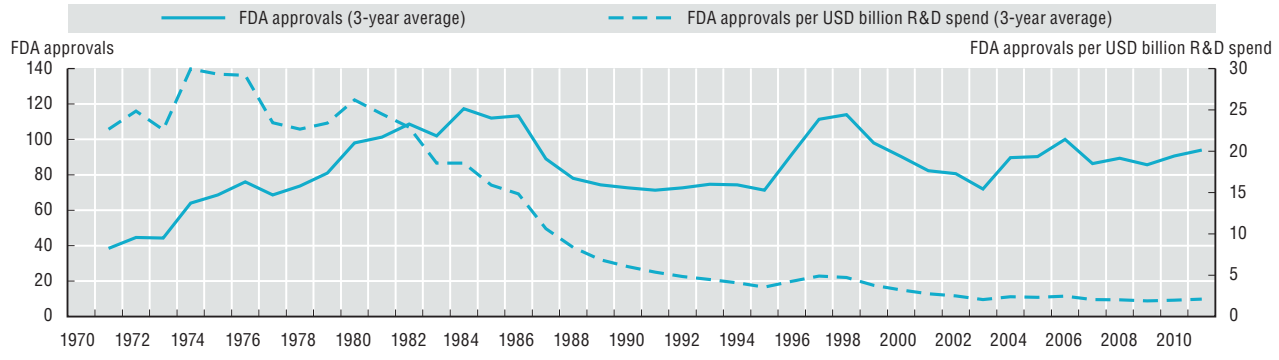
10.15. Business expenditure on R&D in the pharmaceutical sector by region in 2000, 2005 and 2011 (or nearest years) in 2005 USD PPP



Source: OECD Main Science and Technology Indicators Database.

StatLink http://dx.doi.org/10.1787/888933281362

10.16. Annual FDA pharmaceutical approvals, per USD billion R&D spend (indexed to 2008 USD)



Source: Pharmaceutical Research and Manufacturers of America (PhRMA); Food and Drug Administration (FDA); Scannell et al (2012).

StatLink http://dx.doi.org/10.1787/888933281362

Information on data for Israel: *http://oe.cd/israel-disclaimer*

Supporting the competitiveness of the pharmaceuticals sector in the EU

Lowri EVANS

Director-General for the Internal Market, Industry, Entrepreneurship and SME, European Commission

Health matters to everyone. Modern medicine and the health services have made an enormous contribution to increasing life expectancy and quality of life. This is why the "well-being" of the healthcare sector is something the Commission cannot and must not neglect.

The pharmaceutical industry is one of the major players in the healthcare sector and falls - together with the medical devices industry - under the remit of the Directorate-General Internal Market, Industry, Entrepreneurship and SMEs (DG GROW). It is not only an asset for the health of our citizens, but also a major creator of high value jobs. The fact that the pharma industry is located in Europe, and that it is here where the costly research and development of products takes place, gives Europe's citizens access to the latest advances in medicines: the markets where patients benefit first tend to be those where a significant part of the value adding activities occurs. The fact that so much of the industry is based in Europe helps to ensure that its products are closely monitored and adhere to Europe's high-quality standards. In times of world-wide pandemics such as Avian flu or today Zika, a European industry with an integrated value chain is an indispensable asset allowing Europe to make the products needed available to our citizens without delay.

We are facing multiple challenges. Nearly every week the media cover issues related to the high costs of Europe's healthcare systems; often fingers are pointed at the pharmaceutical industry as one of the causes of this problem. Public authorities are called upon to strike a balance between guaranteeing patients' access to state-of-the-art medical treatment and ensuring that incentives are provided for the industry to continue to invest in pharmaceutical R&D to keep the EU a hub for life science innovation. This situation is even aggravated by emerging (often more costly) innovative therapies, increasing expectations of patients and the inherent trend for more healthcare demand as a consequence of an ageing society. The recent press coverage of admittedly very efficacious medicines to treat hepatitis and the ensuing public debate on the price tag attached to this treatment option won't be the last such case. It is fair to assume that the revenues and profits of the pharmaceutical industry will be subject to intense scrutiny by the general public and public authorities.

While there is a consensus in Europe that universal access to medicines is a characteristic of the European social model worth preserving, no satisfactory answer has been given to the issue of how to balance the different objectives with limited financial resources available.

To make things even more complicated, we always have to be aware of the legal situation in the EU, namely that rules affecting pharmaceuticals are set at both the EU and national level. On the one hand the framework for placing a pharmaceutical product on the market, other related issues such as the supervision of products after authorisation, the manufacturing, wholesaling or advertising of medicinal products for human use, clinical trials, the general single market legislation and promoting research are at least partly handled at the European level. On the other hand defining health policies and organising and allocating financial resources (including decisions on pricing and reimbursement of medicinal products) concerning public healthcare are unequivocally enshrined – in Art.168(7) TFEU – as Member States' competences. To overcome the problems arising from often diverging policies in 28 Member States and at the EU level, the Directorate-General Internal Market, Industry, Entrepreneurship and SMEs has advocated an approach addressing the traditionally fragmented way of dealing with healthcare issues and to reduce barriers.

The Commission has always been committed to the dual objectives of ensuring the long-term competitiveness of the European-based pharmaceutical industry and the sustainability of public healthcare systems in Member States. These two objectives are not contradictory; we should rather explore smart ways which allow us to pursue these targets simultaneously and advocate a comprehensive approach harnessing the full potential this sector holds for employment and economic growth as well as modern treatment options.

One way to go about it is to establish cooperative working arrangements bringing together authorities from Member States with representatives of different branches of industry. Contrary to common belief industry does not constitute a monolithic block: producers of generic drugs and the manufacturers of patented products often have conflicting views on certain issues. In addition, patients' representatives, healthcare professionals, trade unions etc. should also be sitting at the table. For this reason about two years ago the Commission established multi-stakeholder workshops, which have allowed the different actors to exchange of views. The Commission has also been active in facilitating the early market entry of safe medicinal products by setting up a joint undertaking, the so called Innovative Medicine Initiative (IMI). It brings together industry and public authorities to facilitate and speed up new product development.

By approaching the problem from all directions, I am convinced that the Commission can make a substantial contribution to addressing the challenges Europe is facing in the field of healthcare.

The Innovative Medicines Initiative – delivering on its promises

Pierre MEULIEN
IMI Executive Director

With the first Innovative Medicines Initiative (IMI) projects drawing to a close, now is a good time to ask if they have delivered on their goals and, more broadly, if they are delivering value for the European taxpayers who provide half of IMI's budget. Measuring the project outputs against the goals of the initial IMI legislation demonstrate that the projects are achieving their goals and making a real difference to medicines development in Europe and beyond. Furthermore, there are signs that IMI projects are starting to have a socio-economic impact.

The first batch of IMI projects was launched in 2009 and they are now coming to an end. It is therefore timely to ask what they have achieved, how they have contributed to the goals of IMI, and what their legacy is in terms of socio-economic impacts.

IMI – improving the drug development process for safer, better medicines

The EU legislation creating the initial IMI programme states that its overarching objective is to 'improve the drug development process' to facilitate the generation of 'more effective and safer innovative medicines'. The legislation also highlights the importance of promoting small and medium-sized enterprises (SMEs) in IMI activities.

Over the years, IMI has developed a set of key performance indicators (KPIs) to track its progress towards these goals. IMI reports on these in its Annual Activity Reports and they show that, in short, IMI is working.

For example, IMI projects have delivered hundreds of tools that are being used to improve the drug development process in many different ways. These include over 450 biological markers with the potential to improve diagnosis of diseases, allow more personalised treatments, and demonstrate the safety and efficacy of treatments. Many projects are in discussions with medicines regulators like the European Medicines Agency (EMA) to formally validate these biological markers. Validation means that results generated using these markers are more likely to be accepted by regulators when assessing new medicines.

IMI projects have also proven capable of setting up platforms and infrastructures that are accessible to the broader research community. The European Lead Factory has created a collection of some 400 000 compounds from both private and public sources and set up a state-of-the-art screening centre. Research groups can apply to access this resource to hunt for compounds that will be useful in their own drug development programmes. The first users report that the results delivered by the project have reinvigorated and accelerated research programmes in areas as diverse as cancer and antimicrobial resistance.

Projects have also developed over 100 laboratory and computer-based tools to make it easier to study diseases while reducing the use of animals in research. For example, IMI cancer project PREDECT has designed complex, three-dimensional (3D) models of tumours that behave more like cancers in the body than simpler, two-dimensional models. Project partners are now using the 3D models in their research.

A number of IMI projects are establishing networks of scientists and/or medical centres that allow large-scale, pan-European studies to be carried out. For example, the COMBACTE project has a network of over 500 sites that is already being used to carry out clinical trials of antibiotics and other studies into antimicrobial resistance. The EU-AIMS project has set up a clinical research network that will help to add to our understanding of autism spectrum disorders, which affect over 1% of all children and for which there is currently no cure.

IMI projects are also involved in the later stages of drug development. In GetReal, stakeholders including health technology assessment (HTA) bodies are investigating how to incorporate real-life clinical data into drug development. The PROTECT project has developed guidance on how to assess and visualise the benefits and risks of medicines. WEB-RADR has developed an app that allows patients, carers and healthcare professionals to quickly and easily report side effects of medicines via their smartphones. The app is currently available in the UK and the Netherlands and a Croatian version will be launched this year. The project is also developing a template of the app that other national medicines regulators can easily adapt for their own needs.

IMI and SMEs – partners in medicines R&D

SMEs are major drivers of growth and job creation in Europe. They are also a key element in the medical R&D ecosystem, and this is reflected in IMI's projects, where they make up 15% of participants. SMEs are benefiting from their involvement in IMI in a number of ways.

Through the ENABLE project, French SME Nosopharm is advancing the development of a novel antibiotic it has developed which is designed to treat multidrug-resistant hospital-acquired infections. In addition to funding, Nosopharm benefits from access to some of Europe's leading experts in antibiotic development, and this in turn will strengthen Nosopharm's reputation within the antibiotic development community.

German SME Taros Chemicals is a project leader in the European Lead Factory. For Taros, participating in an IMI project has delivered many benefits, ranging from an expansion of the company's labs to the acquisition of new skills and a deeper understanding of the pharmaceutical business.

The first signs of IMI's socio-economic impacts

The legislation creating IMI also states explicitly that it should 'provide socio-economic benefits for European citizens'. IMI carried out an initial survey of socio-economic impacts at the end of 2015. One obvious impact is the efficient use of EU funds through

the leverage of private sector investments. Put simply, for every euro invested in IMI by the taxpayer through the EU, another euro is invested by the private sector through its contributions to IMI.

In addition to boosting the competitiveness of SMEs as outlined above, IMI projects have also triggered the creation of new organisations; in many cases, these are designed to continue the work of the project once the funding period finishes. For example, the Open PHACTS project created an online platform that links up diverse databases of information relating medicines, allowing researchers to quickly and easily access, query and analyse data from multiple sources in one go. The project partners created the Open PHACTS Foundation to continue managing the platform. Set up as a charity in the UK, its work is supported by its members.

In a similar way, the PharmaTrain Federation is continuing the work of the PharmaTrain project, which set up training courses on medicines research and development.

There are also cases where project partners (including SMEs and academics) are patenting commercialising products born out of IMI projects. For example, IMI's CHEM21 project is working to reduce the environmental impact of medicines development and manufacture. Project scientists are now patenting a chemical process developed through the project. Elsewhere, researchers from diabetes project SUMMIT are patenting a specialised ultrasound imaging technique that makes it possible to identify people at imminent risk of a heart attack or stroke.

Looking to the future, IMI has tasked a group of independent experts with carrying out a more in-depth analysis of the outputs and socio-economic impacts of IMI's first projects. Their findings will be published in the coming months. Meanwhile, IMI has now launched a number of projects under IMI 2, which has a bigger budget and even more ambitious goals.

For its part, IMI remains committed to ensuring that all of its projects deliver results that will not only improve drug development processes, but improve the lives of patients the world over.

IMI in a nutshell

The Innovative Medicines Initiative (IMI) was launched in 2008 with the ambitious goal of improving the medicines development process and making it more efficient so that patients will have faster access to better and safer medicines. Today, IMI's collaborative projects are delivering promising results in disease areas that are all too familiar to many Europeans, including dementia, infectious diseases, and diabetes. Globally, IMI is recognised as a pioneer of open innovation and a model for successful public-private partnerships in research.

IMI is a partnership between the EU (represented by the European Commission) and the European pharmaceutical industry (represented by EFPIA, the European Federation of Pharmaceutical Industries and Associations). Half of its €5 billion budget for the period 2008-2024 comes from the EU; the other half comes from the industry.

IMI projects address challenges in medicines development that can only be addressed by collaborations involving all relevant stakeholders, including universities, small to mid-sized companies, patient organisations, regulatory authorities, the pharmaceutical industry, and companies from other industries such as imaging and diagnostics. EU funding is only allocated to partners like universities, SMEs, patient organisations, etc. EFPIA companies do not receive any EU funding through IMI, but contribute to the projects 'in kind', for example by donating their researchers' time or providing access to facilities or resources.

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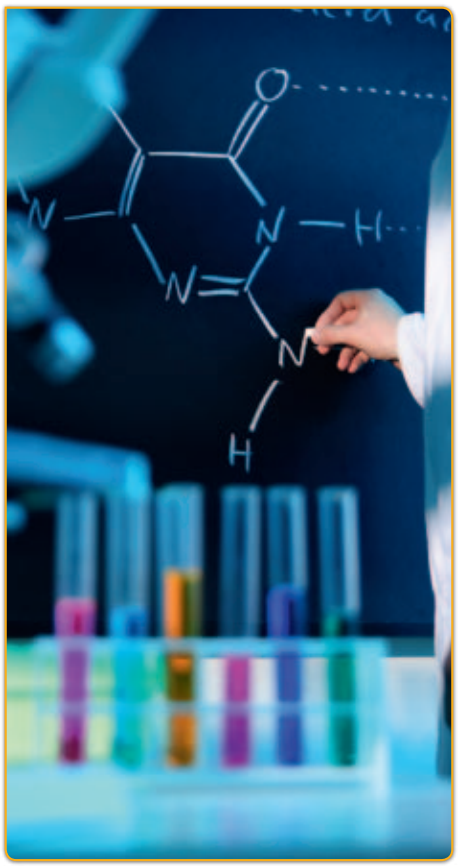
Adapt the ATMP regulation, a need for innovation

Peter LIESE
MEP (EPP group),
Member of the ENVI committee

Modern biotechnology delivers a lot of opportunities for patients, which cannot be cured at all or cannot be treated sufficiently at the current time. To guarantee favourable regulatory environment especially for cell therapy and gene therapy and at the same time assure patients' safety, the European institutions adopted the ATMP regulation in 2007. The purpose of the regulation was never disputed in principle. On the other hand many members of the parliament including myself and many experts argued from the beginning of the legislative process that the current form of the regulation is not appropriate. Unfortunately, we have been proven right. To date only 6 products have been approved by EMA. This is of course partly because innovation was not as successful as we thought, but on the other hand there are also shortcomings in the existing regulation that urgently needs to be addressed. In the area of cell therapy, especially autologous cell therapy producers intend to market the product for a small scale. Many of these companies are SMEs and only active in one member state or even part of one member state together with hospitals. For them the obligation to go for a market approval to the European Medicine Agency (EMA) in London is very burdensome and costly. Unfortunately, this led to a downgrading of promising therapies, so that companies are no longer obliged to apply for authorisation under ATMP. This can definitely not be the purpose of a European regulation. On top of this reimbursement in the member states is quite different and most of the time relatively low. That´s why in my view it would trigger innovation, if we could adapt the ATMP regulation. Companies that only market for a national or regional market, shouldn´t be obliged for European central authorisation. The European Parliament has repeatedly asked the Commission to present a new proposal for this reason but also for another reason. After the adoption of the regulation the charter of fundamental right entered into force and is now legally binding for the European institutions. One important principle is the prohibition on making the human body and its parts as such a source of financial gain (Article 3). This principle is already implemented in the directive on organ donation and it should also be implemented in the case of tissues and cells. That´s why the directive on tissues and cells and the ATMP regulation should be adopted accordingly. It is necessary to promote innovation in biotechnology and abolish regulation, which hinders innovation, especially for SMEs. At the same time, it is important to have a clear framework build on ethical principles.



General Information

Advanced therapy medicinal products are new medical products based on genes (gene therapy), cells (cell therapy) and tissues (tissue engineering). These advanced therapies herald revolutionary treatments of a number of diseases or injuries, such as skin in burns victims, Alzheimer's, cancer or muscular dystrophy. They have huge potential for patients and industry.

The lack of an EU-wide regulatory framework in the past led to divergent national approaches which hindered patients' access to products, hampered the growth of this emerging industry and ultimately affected EU competitiveness in a key biotechnology area.

The EU institutions agreed on a Regulation on advanced therapies (Regulation (EC) 1394/2007), designed to ensure the free movement of advanced therapy products within Europe, to facilitate access to the EU market and to foster the competitiveness of European companies in the field, while guaranteeing the highest level of health protection for patients.

Medical innovation and medicines pricing

Yannis NATSIS
Policy Coordinator,
European Public Health Alliance (EPHA)

The issue of high prices of medicines has become and rightly so, one of the most debated topics across the continent. It is high time policy-makers acknowledged that the exorbitant prices imposed on medicines constitute the main obstacle between a patient and her/his treatment. Even the wealthiest of member states are forced to employ strict rationing methods in order to limit the number of patients eligible for the latest usually most expensive treatments. They fear for the survival and sustainability of their public health system; therefore the "slightly sick" are excluded until their condition deteriorates. Under these circumstances, patient groups compete against one another, they attack the state; complain over high co-payment rates while the public health system struggles to meet the needs of the overall patient population.

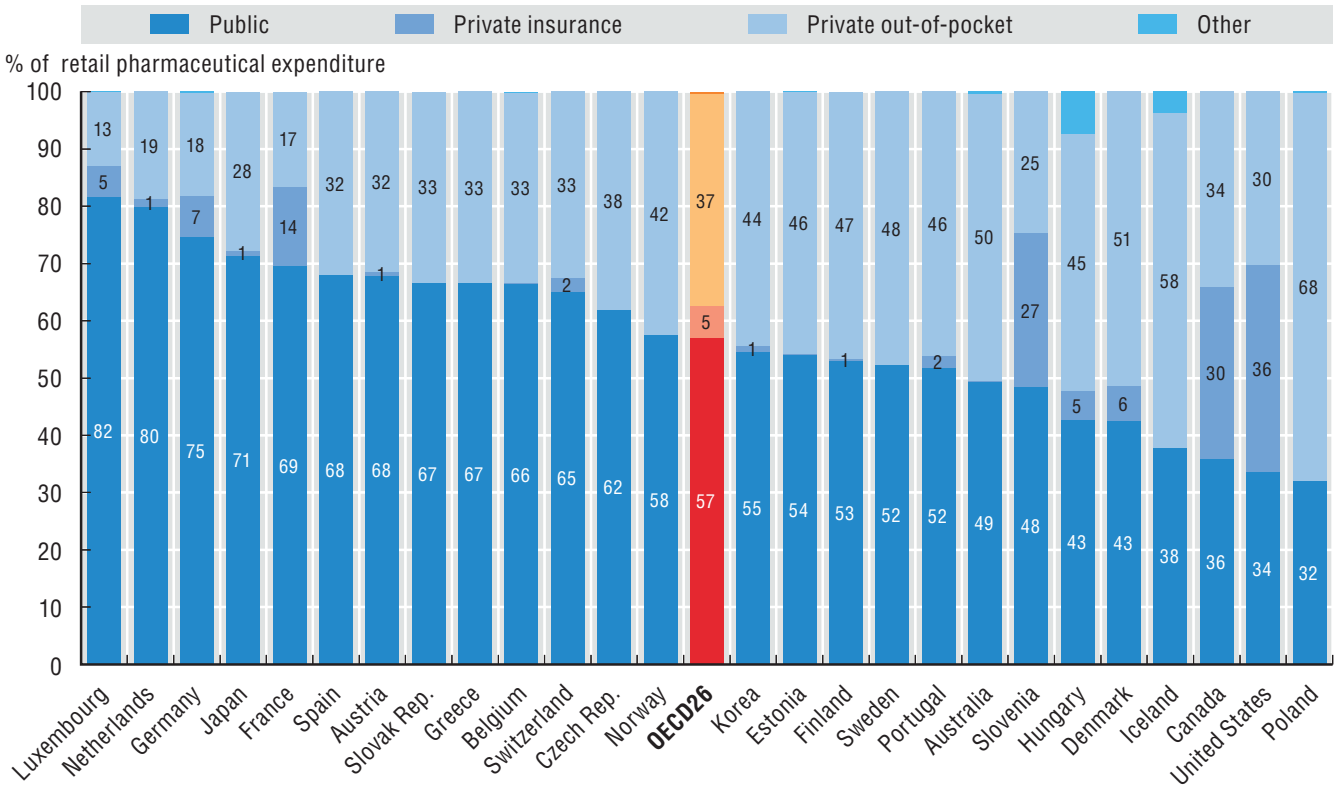
Despite the political noise and the public outcry against Gilead's 1.000$ per pill Hepatitis C drug Sovaldi, the attitude of Martin Shkreli of Turing pharmaceuticals and various other incidents, the pharmaceutical sector stands firmly by its business as usual model which operates according to "the sky is the limit" principle when it comes to the prices of its products.

The Dutch Minister of Health Ms. Schippers whose country holds the Presidency of the EU during the first half of 2016 has boldly listed some of the major flaws of the current model of medical innovation: the abuse of the patent-based monopolies and how they may hinder much-needed competition, the lack of transparency in research & development investment on behalf of manufacturers, the astronomical prices particularly for orphan drugs, the absence of added therapeutic value of new medicines and the public return for publicly-funded research. In light of these challenges, her country appears to be joining forces with Belgium and Luxembourg looking for fitting forms of action.

These developments confirm that there is political momentum but the emphasis on the high prices of medicines does not please certain stakeholders. That is why; there are systematic attempts a) to shift the attention away from the core problem i.e. the pharmaceutical business model which relies on immorally high prices for its products and b) to reframe the debate by talking about other issues such as "earlier and faster access to medicines and innovation". The long-term strategic goal of the proponents of this attempt is to restructure the EU medicines regulatory framework. They conveniently argue that much of the regulation has become too complex, too detailed and with too much focus on procedures instead of real issues. Most worryingly, they stress that it is imperative to review how we evaluate uncertainty and what they mean is to strike a new balance between patient safety and quicker access for patients. Practically, what is sought after is to save companies' time and money by changing the way we develop drugs. The goal is to get medicines on the market much easier and earlier by lowering evidentiary requirements mostly via prioritizing the products' efficacy over safety. This is the spirit of a range of policy proposals such as the Adaptive Pathways pilot project run by the European Medicines Agency (EMA) and strongly supported by the industry, the Priority Medicines (PRIME) scheme and initiatives within the Innovative Medicines Initiative (IMI) to name but a few.

The push for accelerated approvals is not the way forward and does not address the problems patients face in Europe and beyond. For example, it is telling that none of the supporters of adaptive pathways reassures us that medicines will be affordable. Policy-makers should not be misled by these self-titled solutions put forward by specific financial interests. We must seize the political momentum; ask the real questions and highlight the appropriate solutions. Firstly, we need new medicines that offer real added therapeutic value. Independent reviews such as the Cochrane Collaboration, Prescrire and several national HTA bodies point to the fact that most new drugs offer only marginal therapeutic benefits in comparison to the best alternatives already on the market. The industry must move away from this me-too mentality and towards genuine innovation as this will benefit society as a whole. It is up to the regulator to send a strong message to the manufacturers about the quality of innovation it favours rather than focus on lowering standards for marketing authorization. Secondly, Europeans today, we pay for our medicines twice, as a big chunk of medical R&D is publicly funded. Hence, it is essential to have full transparency in R&D costs and in how prices are set while public financing should be complete with strict conditionality criteria that guarantee the public return of public investment. Thirdly, public health needs should dictate research priorities and public funding should be defined accordingly. Fourthly, a level-playing field and a balanced involvement of all stakeholders in decision-making are critical in order to avoid regulatory capture by certain interests. Last but not least, we should always bear in mind that access to medicines is a human right as well as a matter of social justice for millions of Europeans and from their perspective an unaffordable treatment is as good as a non-existent one.

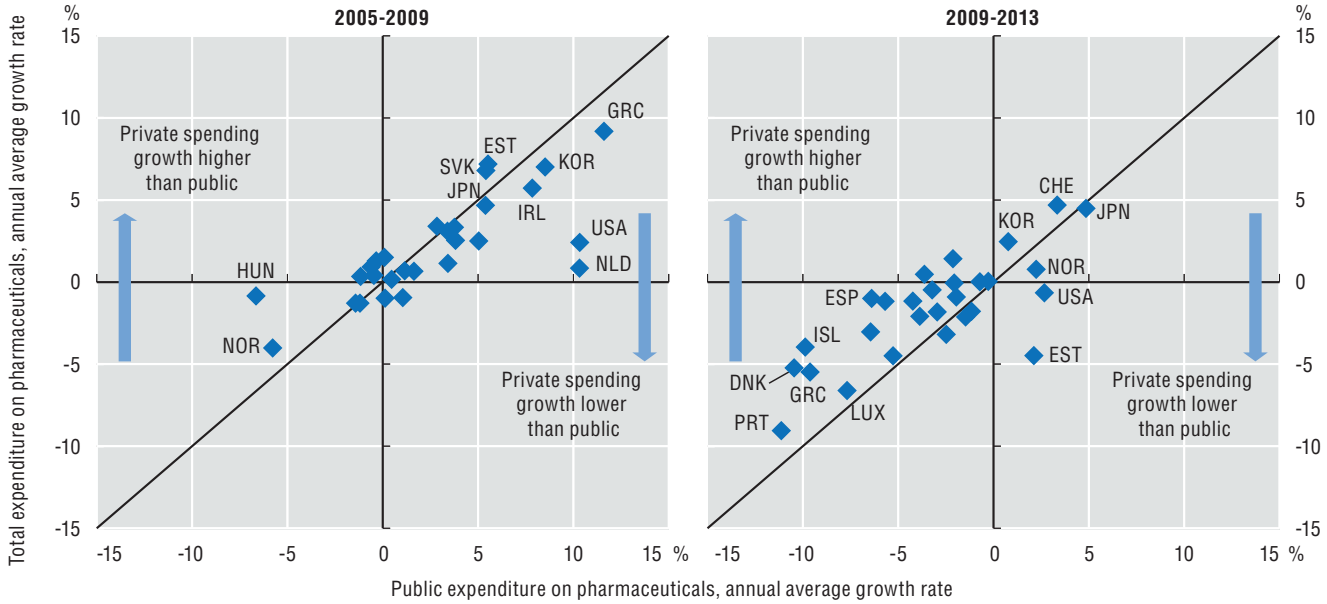
Expenditure on retail pharmaceuticals by type of financing, 2013 (or nearest year)



Source: OECD Health Statistics 2015.

StatLink http://dx.doi.org/10.1787/888933280689

Annual growth in public and total retail pharmaceutical spending, OECD countries, 2005-2013



Source: OECD Health Statistics 2015.

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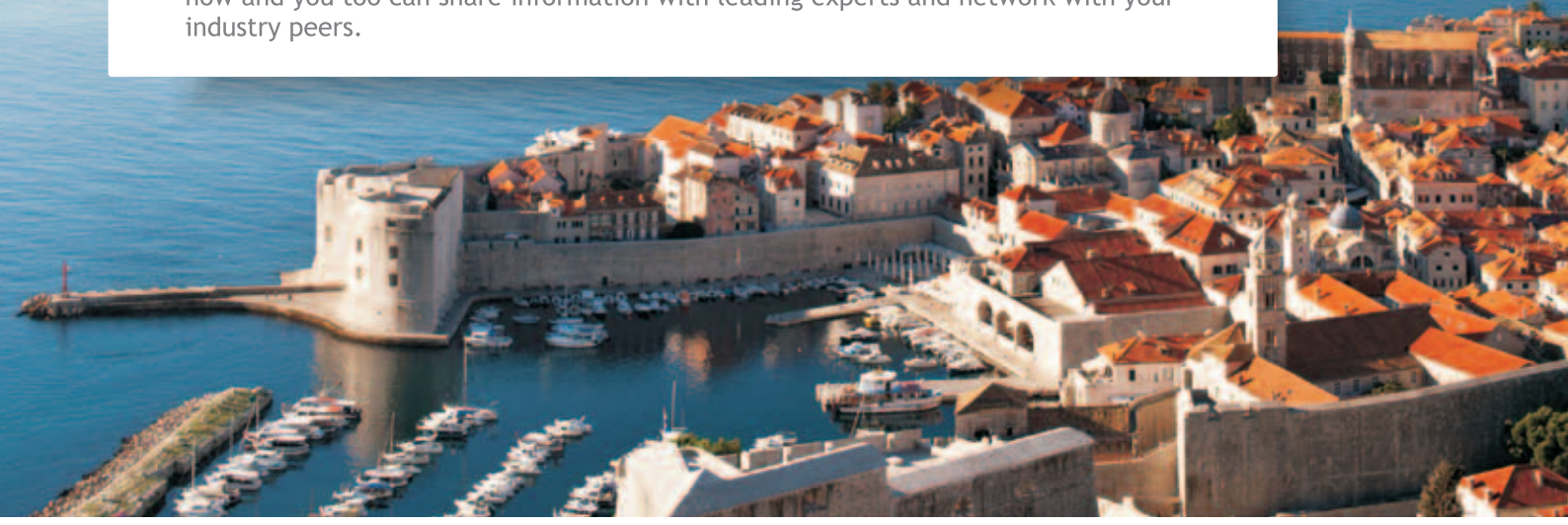

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