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Medicines of the Future:

How to Sustain Pharmaceutical
Innovation and Improve
Access and Affordability?



INNOVATIVE MEDICINES INITIATIVE: EUROPE'S PARTNERSHIP FOR HEALTH.



Antimicrobial resistance

- kills 25 000 Europeans every year
 - costs €1.5 billion to the European economy annually
 - only two 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.



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.



Vaccines

- save 2-3 million lives worldwide every year
 - help millions avoid infection with preventable diseases including diphtheria, tetanus and measles
- IMI's vaccine projects are working to improve vaccines development and deliver better, safer vaccines against flu, pertussis and Ebola.



Diabetes

- 51 million cases in Europe
 - costs Europe €129 billion in 2014
- IMI is investing in six projects working to improve diabetes research and develop tailored diabetes treatments for individuals.

EDITORIAL

Medicines of the Future: How to Sustain Pharmaceutical Innovation and Improve Access and Affordability?

The future of healthcare in Europe depends on its sustainability and flexibility. The European Union (EU) is responsible to approach sustainability through a cost-effective framework that should minimize inequality within and across national boundaries. Flexibility is a consideration of accessibility for all patients, including those carrying rare diseases. In both these objectives, quality is key. Quality in vaccines and other medicines solutions requires months, if not years, of research and development (R&D) coupled with extended periods of rigorous testing. These could be considered barriers to innovation, though these costs ensure that only the very best products are released to patients. However as competition in the medicines R&D decreases, success rates in the deployment of medicines also declines. This means European patients are left with fewer medicines and generally higher costs. The European Commission is acutely aware of the need to redistribute these costs while continuing to motivate large amounts of investment in R&D. The solutions explored in this issue of The European Files maintain patient involvement in innovation as central to a more effective medicines development policy.

Many directives have been taken by the European Commission through the recommendation of a variety of stakeholders. In the case of patient involvement, the Innovative Medicines Initiative is proud to present several programs that have gained traction to provide patients with a respected voice in the R&D process. Programs such as EUPATI and PREFER aim to harness the opinions of patients and

better satisfy their needs. These programs have already seen much success, as development of new medicines is deemed more patient-appropriate and transparent. However the road is long and there are still many governing bodies with medicines authorization that could increase their patient participation through these platforms. In addition, EU member states must consider alternative pathways to best approach the development of new medicines solutions. This may require new long-term cost evaluation frameworks that balance the burden and impact of developing a new medicine. The proper valuation and impact of a new medicines solution is a hotly contested issue when motivating new ways of financing. National healthcare providers must consider large up-front costs that simply cannot be maintained in less developed states.

This inequality in access to new medicines should be smoothed through expanding collaboration across the EU and its member states. The steps taken to strengthen all national decision-makers position and enable them to negotiate better access to medicines.

The EU must balance pressures to improve public health as well as maintain a competitive and sustainable medicines industry. Through a refined focus, a pioneering Europe in healthcare is one that positions the patient as an equal member of medicines innovation. A breakthrough in healthcare necessitates this mindset and approach as this issue of The European Files suggests.

LAURENT ULMANN



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Gearing up to address the challenges of future pharmaceutical innovation



Chris FEARNE

Minister for Health, Malta

A series of activities, initiatives and reports, all aimed at providing solutions as national governments and European institutions struggle in their quest to balance European market growth with access to affordable medicines have taken place over the past months. The year 2016 can be marked as a turning point for medicines policy in Europe. Increasingly, efforts are being made to bring diverse stakeholders together to address what has become an issue of global concern. Europe has an important leadership role to play on the global stage in contributing to the world order that needs to underpin access to innovation for the future.

On 17 June 2016, the Council adopted its conclusions on *"Strengthening the balance in the pharmaceutical system in the EU and its Member States"*. In these conclusions, the Council called upon Member States and the European Commission to improve cooperation on pharmaceutical policy at EU level, while also analysing various aspects of the pharmaceutical system to examine how the balance between public interest such as innovation, accessibility, availability and affordability of pharmaceutical products can be strengthened.

Malta assumed its Presidency of the Council of the European Union on 1 January 2017. Strengthening structured cooperation between European health systems in order

to enhance access to innovative medicines and technologies is an important priority for the Maltese Presidency in the health sector. Achieving a more coherent and coordinated policy approach to pharmaceutical innovation is of vital interest for European citizens and public health as well as for the economic operators. The Maltese Presidency aims to produce Council Conclusions on voluntary structured cooperation among Member States. Innovative approaches to procurement of innovative health technologies including medicines will be addressed in these Council Conclusions.

It is widely recognised that advanced therapy medicinal products (ATMPs) including genetic therapies have the potential to reshape the treatment of a wide range of conditions. Rapid developments in the nature of pharmaceutical innovation are bringing about a renaissance has been likened to the transformations that took place when health systems moved from a pre-antibiotic to the antibiotic era. Today, nobody can imagine a world without effective antibiotics which is why antimicrobial resistance is rightly so high on the global agenda. Currently we are experiencing a transition into a new realm with treatments of conditions previously thought incurable, becoming available. This is all promising and exciting with one major caveat – the price tag attached. Medicines are far more than a mere object of trade insufficient access to effective innovative medicines due to high prices poses a serious threat both the sustainability of national health care systems as well as to the European social model.

Political institutions, regulatory bodies, HTA bodies, health system payers and the industry are gradually converging towards the notion that the traditional models of pricing and reimbursing medicines will not be appropriate for medicines of the future. Alternative business models for the development of new medicinal products against affordable and acceptable costs are being sought. It is important that we venture forward into this new era in a spirit of partnership based on trust and mutual respect for the specific responsibilities of all actors in the pharmaceutical chain as well as Member States competences.

The pharmaceutical pipeline is likely to exert increasing pressure for expenditure growth on medicines. The present asymmetry in the negotiation capacities and information on pricing between pharmaceutical companies and Member States is prompting further Member States to seek European cooperation on a bilateral and multilateral basis. The system of confidential negotiations between the pharmaceutical industry and individual Member States raises several questions about who benefits mostly and the extent to which this is a sustainable model. The advent of personalised medicine with treatments being used for smaller number of patients necessitates that we explore new models to create synergistic and sustainable solutions for patients, payers and the industry. Healthcare expenditure is an investment that enables European citizens to live longer and healthier lives. Yet in order to gear up for increased levels of investment, we must build systems characterised by transparency and capable of demonstrating value for patients, families and society. Outcomes based managed entry agreements (OBMEA) are being promoted as mechanisms that allow the price and reimbursement conditions of medicines to change over time in response to health and financial outcomes in daily practice. This is however a major undertaking and several aspects need to be clarified with robust data governance systems being established at the start. The piloting of such initiatives through an inter-governmental approach merits further consideration. Member States should support joint work to generate evidence on the effectiveness of treatments in the health system. This could well be accompanied by capacity building for reinforcement of negotiations capacities within health systems.

It is timely to consider launching a high-level strategic dialogue with all the relevant stakeholders gathered together in a single forum to avoid further duplication and fragmentation of activities. This forum should seek to combine clinical, public health and business expertise in order to identify the macro governance models and micro management solutions which we need to embrace in order to ensure that all European citizens, irrespective of the level of socio-economic development of their country, can benefit from the added value of innovation.

Ensuring universal and affordable access to safe and innovative medicines



Vytenis ANDRIUKAITIS

EU Commissioner for Health and Food Safety

We are entering into a new era of innovative medicines and medical devices in the EU, with news of promising breakthroughs virtually every day. This should be good news for patients, particularly those who suffer from diseases that have so far been extremely difficult to treat, such as rare cancers, lung diseases and Hepatitis C. However, such innovations often come with hefty price tags and remind us that there are still unacceptable inequalities in the EU when it comes to healthcare.

Pharmaceutical pricing and reimbursement is the competence of individual EU countries, and today there are still wide variations between different health systems. However, several groups of countries have already started exploring possibilities for jointly negotiating prices for expensive drugs. Belgium, the Netherlands, Luxembourg and Austria are working together, for example, and Romania and Bulgaria have also recently struck up an agreement.

Unequal access to innovative medicines is a hot topic these days, and Patients can feel justifiably outraged if they are denied a breakthrough treatment due to its cost. Better pricing mechanisms can help bridge some health inequalities we still see in Europe today and also make our health systems more sustainable. Although this is a national matter, the Commission is committed to supporting

and assisting EU countries so that their health systems become more effective, accessible and resilient.

As a starting point, EU-level forums give EU countries the opportunity to discuss together how to increase patient access to innovative medicines and to reflect on questions such as: How can we create partnerships between the pharma industry, EU countries and payers? How can we ensure that patients' needs are met and that profit does not play an exclusive role in medicine access?

Such topics are not only discussed by national Health Ministers, practical solutions to ensure patient access to innovative medicines are explored in the Safe and Timely Access to Medicines for Patients 'STAMP' Expert Group. Politicians and experts agree that it does not only depend on optimisation of authorisation procedures, but is also linked to Health Technology Assessment (HTA), where there is much potential for cooperation at EU-level.

High-quality assessments of health technologies provide vital evidence-based information to support decision makers in allocating their resources to ensure sustainability of health systems and that real innovation reaches patients. A recent study for the UK¹ which focused on 10 health technology assessments concluded that savings of approximately £3 billion could be achieved in that country alone if the recommendations from HTA reports were followed.

The potential EU-wide benefits are enormous, which is why all our efforts are focused on building on the knowledge base developed by the voluntary EU-wide network on HTA so we can strengthen and enhance EU cooperation in this area on a permanent and sustainable basis. The Commission has recently conducted a public consultation, to help us shape pan-European cooperation on HTA, and we intend to present the results of the consultation this Spring and to put forward a policy initiative before the end of the year.

Whilst sustainable EU cooperation on HTA can contribute to speeding up patient access to innovative healthcare, a number of other EU tools can contribute to addressing the challenge, namely: incentives for orphan medicines, the EU joint procurement mechanism, and the Health Programme.

If access to affordable medicines is difficult for ordinary patients, think of those who suffer from a rare disease that affects fewer than 5 in 10,000 people. The incentive to develop so-called 'orphan' medicines for an individual rare disease is obviously low. To remedy the situation, EU legislation provides rewards and incentives such as fee waivers for the regulatory procedures or a period of market exclusivity. With 129 Commission-authorised orphan medicines so far, the results speak for themselves.

Another useful tool that I regularly urge EU countries to seize upon is the Joint Procurement Agreement (JPA) which I have just mentioned². Most EU countries have now signed the JPA and can in principle band together to buy vaccines, diagnostic kits, medicines and other items, and potentially benefit from more favourable conditions.

Finally, the EU Health Programme supports research and information tools that can benefit all countries. EU-funded projects have provided a better understanding of how medicine pricing could be applied to minimise negative effects on both patient access and health budgets.

Universal access to innovative medicines is a complex issue depending on a range of factors – from research and development, to marketing authorisation procedures, to HTA, and pricing and reimbursement decisions. I intend to continue supporting Member States in providing timely and affordable access to safe and innovative medicines to all patients in every way I can.

1 Guthrie S, Hafner M, Bienkowska-Gibbs T and Wooding S, Returns on research funded under the NIHR HTA Programme: Economic analysis and case studies. RAND Report RR-666-DH, 2015.

2 The Joint Procurement Agreement was established by Decision 1082/2013/EU on serious cross-border threats to health: http://ec.europa.eu/health/preparedness_response/joint_procurement_en

Citizens' access to pharmaceutical innovations



Dolors MONTSERRAT

Spanish Minister for Health, Social Services and Equality

Providing healthcare and essential medicines to citizens is a priority for the healthcare systems of the European Union. For years, the only barrier to access to medication was obtaining a marketing authorization. However, different factors—such as globalization of the pharmaceutical industry, unrelenting scientific progress, citizens' right to the best possible health results when they are ill, ageing, the challenges of rare diseases, and personalized or precision treatments—have made the sustainability of healthcare systems a new consideration that must be taken into account when addressing access to medication. To talk of innovation and of access to medication simultaneously is by no means contradictory. We must maintain our conviction and our drive to make innovation, access and sustainability compatible within healthcare systems, in the interests of our citizens.

Innovation in the pharmaceutical industry requires a suitable environment. The European Union must therefore offer the right conditions for innovation to take root and flourish in the region. For the purpose of this article, we will provide three examples of current mechanisms that help innovation to materialize and prosper in the EU. The first is the Innovative Medicines Initiative (IMI), a public-private initiative to foster development of improved, safer medication for our citizens. The second is Regulation No 536/2014 of the European

Parliament and of the Council of 16 April 2014, on clinical trials on medicinal products for human use, which will be fully applicable in the second half of 2018. This regulation will make it possible for the EU to increase the number of clinical trials of medication that has been developed in Europe. This will benefit us all, by promoting a vibrant and active health science industry, but also by undertaking clinical trials in Member States, thus providing patients who have run out of options with a means of access. The third instrument is the framework of aid that the network of European medicine agencies and the EMA itself offer to small and medium-sized enterprises, to maximize successful development of innovative products that can have a significant impact on the health of our citizens. The network's Innovation Task Force, and EMA initiatives such as PRIME (Priority Medicines) aim to foster development of high-impact medication and attract capital from investors, to prevent a lack of experience or of investment from delaying the launch of a product or perhaps even keep it from ever reaching the market—something which can be prevented in the initial stages of development by proper regulatory support.

Once innovation has been achieved, attention must then turn to the instruments that enable access to medication, whilst keeping in mind that this is not a case of all or nothing. Insight into medication grows as its development advances, allowing marketing authorizations to be issued. We must therefore make it possible for medication to reach the market as soon as possible, but with sufficient experience and knowledge to allow authorizations to be issued and subsequent decisions to be made. However, this does not mean that access should be delayed, rather that it should be appropriate to the level of insight into the medication. For this purpose, we have access mechanisms that can be bolstered, thus increasing Europe's competitiveness as a hub for clinical trials, but also opening the door for initiatives such as compassionate use of medication that is being researched or authorization through managed entry schemes, including results-based payments and extensive use of records.

Finally, if this innovation and access is to be accompanied by sustainability, we must focus all of these mechanisms on the value

of the medication. With this in mind, all of the actions linked to this value must be integrated. Notably, the Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States form the backbone of this effort. The goal is to take advantage of synergies between regulators, HTA (Health Technology Assessment Agencies) and payers, whilst respecting their specific responsibilities and Member States' competences, and, at the same time, eliminating duplications in order to ensure that patients have timely and affordable access to innovative medicinal products.

Ensuring our citizens' access to pharmaceutical innovations is a goal of paramount importance that must successfully combine development, access and sustainability. Solutions will only be found if all the parties involved work together, finding the right channels to advance swiftly towards new global and local model, and aligning the decision-making processes of the parties involved without limiting their competences, but also without jeopardizing the validity of the decisions made at each point in the chain. It is possible to identify innovation in each of our countries, favour development through all stages until a product is authorized, and reinvest this innovation to generate health benefits for our citizens, all without losing sight of the viability of healthcare systems. We must unite with this aim in mind.

Keeping the focus on patients' wellbeing – how regulatory tools can help patients in need to access new medicines earlier



Guido RASI

Executive Director of EMA

Medicines regulation must put the needs of patients at the centre of everything it does. This means on one hand that we protect patients from harmful side effects of medicines as much as we can. On the other hand, it is also our role to encourage the development of new medicines to give access to new treatments to patients who have no other options.

At the European Medicines Agency we are committed to ensuring that patients have timely access to beneficial medicines, particularly those that address an unmet medical need or are of major interest for public health.

Scientific advancements made over the last 40 years have vastly increased our knowledge about diseases and their causes, creating many new opportunities for the development of medicines. At the same time, we also see that in some disease areas, for example infectious diseases and rare cancers, the development of new therapies has become highly complex and lengthy, while there are still many patients who are in desperate need of treatments. Therefore, we are asking as regulators 'how can we improve the system in a way that would work also for patients with urgent needs?'

The classic drug development paradigm is built on the 'block-buster model'. It works well for big sellers for large target populations like statins and antihypertensives, but does not work optimally for patients who have no or only unsatisfactory treatment options. They often rely on 'non-conventional' medicines, where treatments are more urgent, patient

groups smaller and generation of robust data is more complicated.

As regulators we have a responsibility to make sure that the system works for all products – no matter how cutting edge they are. Therefore, we need to consider new approaches of medicines development.

One of the approaches we have been exploring since 2014 are adaptive pathways, a new concept of medicines development. Adaptive pathways uses a stepwise approach, permitting approval of medicines in small, tightly-defined populations until more data are available and allows patients who have no or only limited access to medicines to benefit from scientific progress as early as possible without compromising their health and wellbeing.

This concept of medicines development and data gathering is not meant to be used for all medicines, but only for medicines that are expected to have a significant clinical impact for patients with high unmet needs and where traditional data gathering methods, e.g. large randomised controlled clinical trials might be difficult to apply. It involves working with the full range of relevant stakeholders at an early stage in the development process to proactively plan the most appropriate ways of obtaining evidence and also identifies the best tools to generate that evidence. This may mean making more use of observational, or 'real-world' data in addition to data from randomised controlled trials, especially where these trials are not practical.

Adaptive pathways are described as a concept or an approach, because they are not new regulatory routes for medicines and are strictly speaking not separate pathways. Medicines will still be authorised through the legal routes already in place, applying the same rigorous standards of benefit-risk assessment. The difference is in the way medicines development will be planned to better meet the needs of patients with serious conditions for whom there may be no suitable treatments.

Between 2014 and 2016, we conducted a pilot project to explore the practical implications of the adaptive pathways concept with medicines already under development. We invited companies to submit ongoing medicine development programmes which fulfilled the characteristics of adaptive pathways: a staggered approval from small, restricted patient populations to increasingly wider populations, a binding plan of post-licensing

evidence gathering and involvement of key stakeholders, such as HTA bodies in the process.

The pilot showed us that adaptive pathways can support medicine development in therapeutic areas where evidence generation is challenging, such as infectious diseases, Alzheimer's disease, degenerative diseases and rare cancers. It also demonstrated that the approach can bring together multiple stakeholders - regulators, HTA bodies, healthcare professionals and patients - to agree on a prospective plan to generate data on a medicine across its lifespan in areas of unmet medical need.

The pilot also showed us that not all medicines are suitable for adaptive pathways. In fact, we rejected the majority of applications and found only a relatively small number of medicines suitable for this development concept.

Moving forward together with stakeholders

The adaptive pathways concept has generated considerable interest among our stakeholders. While some have supported the concept because of its potential to improve access to new medicines, others have voiced concerns about its possible impact on standards of evidence for medicines approval in the EU. Much of the discussion has centred on how data are to be generated and evaluated for new medicines and whether the goals of adaptive pathways are feasible.

It is critical that we explore and develop any changes to the medicines development process in collaboration with our stakeholders. Their feedback is vital to ensure that any new approach works optimally for everyone involved in the process.

This is why we, in collaboration with the European Commission, held a workshop in December 2016 to tackle important questions arising from the pilot, including how best to address patients' needs and expectations, how to generate appropriate data to aid medicines evaluation and how to ensure that the high standards for approval in the European Union continue to be met. We have some way to go and will keep exploring to find solutions that work for all beneficial innovations that science brings, for all our stakeholders, and that also honour the urgent medical needs of patients.

Towards a new concept: Value Informed and Affordable prices for medicines



Lieven ANNEMANS

Professor of Health Economics, Ghent University

At the OECD Ministerial Meeting on 'Next Generation of Health Reforms' (17 January 2017), Ministers concluded that several new generation treatments are on the one hand very effective but are on the other hand very costly and have significant budget impact and wider implications for our health systems.¹

In search for a solution for this dilemma, it is sometimes argued that prices of innovative medicines should better reflect investments for Research and Development (R&D), a logic which is sometimes referred to as "cost plus pricing". Although this approach might at first sight seem fair, it raises a number of issues. Firstly, it may lead to the wrong incentives, in that the higher the R&D costs, the higher the price which could be justified. Secondly, investment costs for medicines that eventually do not make it to the final stage (because of insufficient effect or due to toxicity, or other reasons) must be amortised and factored into the cost of R&D, which may then lead to a perverse situation where a company with many failures could justify a higher price for a few products that make it to market authorisation. Finally, this approach does not sufficiently encourage true innovation. Irrespective of the benefit to patients, reward will be according to R&D costs.

A better approach is to start from the principle that decisions on pricing and reimbursement for innovative medicines should

account for the added value that they deliver for patients and society, the so called value based pricing. Value can thereby be defined as "the importance, worth, or usefulness of something".² This principle is based on the general economic concept that prices of new goods indicate the difference between what currently available goods offer and the outcomes that the new goods can provide.³ High value then originates from substantially better treatment outcomes versus the actual standard of care. However, better outcomes should not be the sole criterion. For instance, from the work of Erik Nord, it appears that societal willingness to pay for new treatments is dependent on the degree of severity or suffering associated with the current situation.⁴ Value should therefore be defined by both disease and treatment related characteristics.⁵

But value does not necessarily mean "value for money". Price and reimbursement levels of medicines should correspond with an acceptable value for money from a societal perspective. This means that the cost-effectiveness, i.e. the ratio between the net cost of the treatment and the net health benefits always needs to be calculated. Net cost means that predicted savings or additional costs elsewhere in the system or in society are explicitly taken into account. In the interpretation of cost-effectiveness it is then important to have societal thresholds: the maximal amount of money a society is willing to pay for gaining healthy life years needs to be made explicit.

Moreover, decision makers should also systematically take into consideration the budget impact and affordability for the healthcare system. Indeed, even if a treatment is cost-effective, it does not mean automatically that it is affordable.⁶ This is undoubtedly a matter of opportunity cost. Putting too much money in one basket, i.e. one disease, takes away the opportunity to help other patients. Budget impact analyses are therefore required to assess the extent to which the healthcare system can afford to pay for the innovation. In this scenario, the possible offsets elsewhere in the system are to be taken into account as well.⁷

Bringing all the above together, this means that the abovementioned societal thresholds need to be modulated depending on the disease burden⁸ as well as on the budget

impact of the innovative medicine.⁹ Hence, for a treatment in an area with a high burden, and with a low budget impact, the societal willingness to pay for additional health outcomes should be higher.¹⁰ The opposite is true for a treatment in a disease with low burden and a high budget impact. Of course, specific characteristics of each country, such as ability to pay, epidemiological and cultural factors and societal values play a prominent role here.

When healthcare payers communicate explicitly about the societal limits of value based pricing, and how they are modulated in function of disease burden and budget impact it should be possible to reward value and at the same time account for affordability. This approach can be called *value informed and affordable prices* and may become a solution for the current dilemma.

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9 Griffiths EA et al. Acceptance of health technology assessment submissions with incremental cost-effectiveness ratios above the cost-effectiveness threshold. Clinicoecon Outcomes Res. 2015 Aug 31;7:463-76

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EU incentives for Innovation in pharmaceuticals - especially needed for human antibiotics



Peter LIESE

(EPP Group), Member of the ENVI Committee

Too many people in Europe die every year due to antibiotic resistances. The EU must react and needs to find solutions.

According to the World Health Organization (WHO) 25.000 people die in Europe every year because antibiotics are powerlessly confronted with fast developing resistances. Having used too many (and too often the same) antibiotic pharmaceuticals, resistances

could develop and are now becoming a major and alarmingly health issue. Some experts fear that we are entering a so called post-antibiotic-era and WHO experts and the European Centre for Disease Prevention and Control (ECDC) warn us, because the amount of antibiotic resistances nearly doubled in a few years in some regions.

We need new strategies to fight antibiotic resistances. In my opinion the European Union needs to act with a twin-track strategy. Meaning on the one hand finding strategies to reduce the use of antibiotics. In 2015 started, for example, a contest, initiated by Horizon2020, of which aim it is to find solutions for a better use of antibiotics. Especially rapid test methods for finding out whether an antibiotic therapy is really needed are necessary.

On the other hand we need to support pharmaceutical research for finding new antibiotics. Although it is very important to reduce the use of antibiotics and thus act preventively, we also have to be able to react and to treat patients. They can be helped by using new and better antibiotics.

Big pharmaceutical companies cannot set the standards and determine the goals of research in terms of looking for the most lucrative sectors that's why no new antibiotics

entered the market for many years. Therefore, the European Union needs to provide best conditions for excellent research, motivated by the claim to improve patient's treatments. We must not forget what research is for - nothing but for human beings.

We know the problem of again and again new developments of antibiotic resistances not only in human medicine but in veterinary medicine as well. We have a lot of scientific evidence that antibiotic resistant bacteria that emerge in animals is creating problems for humans e.g. when farmers or veterinaries that carry this bacteria entering a hospital. Here Europe is taking action. The European Parliament already agreed on a Commission's proposal to tackle the problem. We need to assure a prudent use of antibiotics while at the same time develop new antibiotics. We hope to agree on the proposal with the council of ministers soon. But in my view action in the field of human medicine is even more urgent.

Why giving incentives to the industry when they develop a new antibiotic for animals and not doing the same for a company that develops new antibiotics for humans? I cannot see any convincing reason to do so, that is why I urge the European Commission to make a corresponding legislative proposal as soon as possible.



Paediatric Regulation - A Better Application for More Efficient Incentives



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The Paediatric Regulation was adopted to encourage the development of paediatric medicines and reduce off-label use of medicinal products in children. Medicinal products were not developed for children, mainly due to insufficient return on investment considering the difficulty and costs of paediatric development. The European legislator considered that the issue was similar to rare diseases, i.e. too small population and expensive, long and challenging trials, and thus gave a similar response. As the industry did not naturally invest in paediatric medicines, an incentive had to be provided to trigger investment.

Determining the right incentives was not easy. The legislator opted for an extension of the existing intellectual property (IP) protections as had been done in the U.S. The incentive had to be European. The supplementary protection certificate (SPC) was the only European right, and seemed an even better choice as the paediatric regime sought to integrate paediatric development into adult development and so targeted more the future than the past. The primary incentive would be an extension of the SPC term.

The Commission proposed a six month extension on the grounds that another six months could be gained in the U.S. with the same studies and that the impact assessment had calculated an average additional

investment of 4,000,000 €, which six months of SPC protection would rightly compensate. But not all substances are patent-protected. For no longer patent-protected products, an IP extension was not an option. Neither was reimbursement of actual investment costs, the calculation of which would be too challenging. A new incentive was created in the form of a new category of MA, the PUMA, which would benefit from a self-standing 8+2+1 years of data exclusivity. Moreover, a special EU fund - the MICE - would be created to invest more public money in paediatric research. Orphan products, which are usually not protected by patent, would benefit from an extension of market exclusivity, the special IP protection for orphan products. Oddly, no incentive would reward paediatric research in new products that are not patent-protected (except orphans).

The paediatric system proposed by the Commission was not perfect. In particular, it would be mandatory (unlike the orphan or U.S. paediatric system), and a PIP would have to be proposed at a time during the development cycle when the attrition rate for the adult product is still more than 80%. Nevertheless, the prospect of being partly compensated for the paediatric development, the positive U.S. experience and probably the trust in a reasonable application of the rules, led the industry to push for the adoption of the Paediatric Regulation.

Ten years later, expectations have clearly not been met. On the one hand, the actual average additional cost for paediatric development is not 4 but 20 million €. ¹ On the other hand, most paediatric investments have not been rewarded; only 45 rewards have been granted in ten years (39 SPC extensions, 3 market exclusivity extensions, 3 PUMAs), i.e. less than 50% of the completed PIP and 5% of the agreed PIPs. And the same studies cannot always be used to claim the incentive in the U.S. as FDA and EMA requirements are different.

What went wrong? The practical application of the Paediatric Regulation. First, the adult condition was used as reference for the scope of the PIP although the rules - and the impact assessment - had been based on the assumption that the reference would be the adult indication. As a result, less adult data could be used or extrapolated for children, and more specific research was necessary. And the average additional investment went up from 4,000,000€ to 20,000,000€. Secondly, the necessary foundation of basic research and understanding of many paediatric diseases was inadequate to embark into paediatric medicine development. So, PIPs included requirements related to paediatric research as a basis for paediatric development, and the requirements for PIP studies increasingly became more and more stringent. The limited pool of potential children available to participate in clinical trials and the competition of similar programs for the same population, intensified the challenges. And completion of PIPs and hence granting of rewards suffered significant delays. Some PIPs even have a completion date that falls after the expiration of the SPC or market exclusivity. The problem is, of course, worse for PIPs related to rare diseases or to already authorised medicinal products. For the optional PIPs (PUMAs), the current pressures on national healthcare budgets do not support the objective of the Paediatric Regulation. The continued off-label use of (adult) generics, which discourages companies from investing in paediatric development, has not been addressed, and the rare companies that did invest in paediatric development, were denied reimbursement or have to compete with non-authorised products on the market. In addition, the MICE was not created to support academic research into off-patented molecules.

How to fix it? The current climate does not seem conducive to incentives for paediatric development. The Council has called for a general review of incentives to the pharmaceutical sector, ² and MEP have questioned the functioning of the Paediatric Regulation, primarily in light of the few paediatric

¹ Commission Report on the Paediatric Regulation (Article 50(3)) – Consultation document, 14 Nov. 2016.

² Council conclusions on strengthening the balance in the pharmaceutical systems in the European Union and its Member States, 23 July 2016.

medicines available in oncology.³ Yet, it remains important to incentivise investment in paediatric development adequately as the number of PIPs under investigation is impressive.

First, it is important to address the criticisms about the functioning of the Paediatric Regulation as incentives are all the more important if regulators determine the scope of PIPs on the basis of the mechanism of action of the active substance rather than the adult condition.

It is correct that the Paediatric Regulation has only generated a few oncology products for children but not because of the connection between paediatrics and adults. We first note that the EMA Policy on the Scope of PIP - adopted in 2012 - states that the mechanism of action will be used in certain cases, in particular in oncology; in short, the mechanism of action has been used for determining the scope of PIPs for more than four years now (and not only in oncology). The main reason for few paediatric oncology products is that the development of a new medicine takes longer than a decade and scientific breakthroughs in oncology are very recent. Another reason is the complexity of paediatric development and demanding study requirements for oncology-related PIPs. The paediatrics – adults connection *will* generate many oncology medicines for children in the coming years - see the EMA ten-year report on the Paediatric Regulation (see box). And the Paediatric Regulation does not envisage a disconnect between adult and paediatric development. To the contrary and for good reasons. On the one hand, ethical rules require pharmaceutical companies to test new molecules in adults first, which justifies the granting of deferrals to start paediatric development. On another hand, paediatric testing in a therapeutic area different from the adult therapeutic area, is much more expensive and time consuming than paediatric testing in the same therapeutic area. The only caveat is if the company decides not to test the substance in adults first; understandably, very few companies are willing to take that risk from an ethical or liability perspective. At the same time, it leads to the development of paediatric medicines in areas with no market for adults and thus to inadequate return on investment due to the small population size. More generally, the health regulators' role is not to direct private pharmaceutical companies' investment (and assume the liability thereof in case the investment jeopardises the company's survival).

In short, the criticisms about the functioning of the Paediatric Regulation show that a better application is needed not only of the 'PIP system' but also of the 'incentive system' as adequate rewards become even the more important if regulators enlarge the scope of PIPs on the basis of the mechanism of action. It should also be noted that the actual average spending on paediatric trials is five times more than initially expected while the incentives have remained unchanged.

A better, more efficient application of the SPC and market exclusivity extensions is tied to a better application of the PIP system, i.e. an application that allows a quicker completion of PIPs. An attractive PUMA is an important complement as most medicines on the market and used off-label in children, are off-patent medicines. The creation of the complementary public funding pool MIDE as should help developing more paediatric formulations based on well-established use in children. So would more cooperation from the Member States in reimbursing or otherwise privileging authorised paediatric medicinal products over off-label uses, in any form (adult generics, preparations or 'Specials').

Let us hope that in the upcoming debate on paediatrics or on incentives, our institutions will not lose sight of the importance of better engaging the pharmaceutical industry in paediatric development, among other ways,

by ensuring a more efficient application of incentives, thereby restoring the balance between investment and rewards. The value of innovation for society requires such a balance, as the success of the Orphan Regulation clearly illustrates.

Oncology is among the diseases that are most covered by PIPs, due to many cancer medicines being under development for adults.

"There are overall 83 oncology PIPs (83 / 859 = 10% of all PIP decisions as of December 2015), and these are for 68 anti-cancer medicines. These 68 anti-cancer medicines represent more than 30 different mechanisms of action (based on the ATC code and the scientific assessment by the PDCO). The main cancer types being studied in 41 out of the 68 PIPs for anti-cancer medicines are those which primarily affect paediatric patients (e.g. acute lymphoblastic leukaemia, Ewing sarcoma, medulloblastoma, neuroblastoma, rhabdomyosarcoma). In fact, 14 out of these 41 PIPs are intended to identify and investigate a childhood cancer as therapeutic target for the medicines' mechanism of action." (EMA Ten-Year Report on the Paediatric Regulation, p.57)



³ European Parliament resolution on the regulation on paediatric medicines, 13 December 2016.

Paediatric Drugs: Improving Regulation for Better Application



Glennis WILLMOTT

MEP (S&D), Member of the ENVI Committee

Every year, 35,000 children and adolescents in Europe are diagnosed with cancer and, while survival rates have improved, 6,000 young people still die from cancer each year. Cancer remains the leading cause of death by disease for children in Europe.

In the last 20 years, great strides have been made in our understanding of cancer and new, innovative treatments have been developed. However, this progress has not been reflected in treatments for paediatric cancers, where drug development lags far behind that for adult cancer; those treatments that are available cause severe side-effects in two thirds of paediatric cancer survivors.

One reason for this is that for paediatric cancers, as with other rare diseases, the number of patients is comparatively small and pharmaceutical companies are therefore often reluctant to invest in research as the return on that investment will be relatively low. In addition, carrying out paediatric trials can be more costly and complicated due to the ethical issues involved.

To try to address this problem, in 2007 the European Union adopted the Paediatric Medicines Regulation. The legislation required pharmaceutical companies to draw up Paediatric Investigation Plans (PIPs) for all new medicines they develop thus ensuring that new medicines were explored for their potential to treat paediatric conditions. It's fair to say the

Regulation has had some success: since 2007, more than 800 PIPs have been agreed, with 41 medicines developed with a specific paediatric indication and a further 120 where paediatric dosing has been improved.

However, the impact of the legislation on paediatric oncology has not been as promising and only two innovative, targeted anti-cancer drugs have been authorised for paediatric indications. One of the main reasons for this is that the legislation grants PIP waivers for medicines that have been developed to treat a condition that does not occur in children. As most adult cancers do not occur in children and vice-versa, many new oncology treatments receive waivers and their potential to treat paediatric cancers is not investigated.

On the surface, this seems to make sense; no one wants to see children subjected to unnecessary clinical trials for drugs that have no chance of helping them. However, two different types of cancer may be caused by similar molecular abnormalities, so even where a drug has been developed to treat a cancer that only occurs in adults, the mechanism of action of that drug may be still be effective for a paediatric cancer. As just one example, Crizotinib is used in the treatment of ALK+ lung cancer, which does not occur in children. The molecular abnormalities that cause this type of cancer have however been observed in a number of paediatric cancers, such as lymphoma and sarcoma, but the developers received a paediatric investigation waiver and so this potentially life-saving medicine has not been explored for its potential to treat children with cancer.

Researchers estimate that in first five years after the Paediatric Regulation came into force, 26 new anti-cancer drugs developed for adult conditions had potential to treat paediatric conditions but over half received a waiver. So, while it's clear the regulation is needed, it also needs improving.

The European Commission has recently carried out a public consultation on the Paediatric Regulation and is due to publish a report on the legislation's impact later this year. This is a key opportunity to make the case for the revision that is needed to ensure the legislation is really working. Together with the parents' organisation, Unite2Cure, I've

been calling for the Commission to amend the legislation so that the decision to grant a waiver is based on a drug's mechanism of action and the biology of a cancer, and not just the type of condition.

This isn't the only change needed. Paediatric Investigation Plans are often started late in a drug's development as investigators wait for it to show promise in adults first; similarly there's nothing to stop investigators ending a promising paediatric trial early if the drug isn't delivering the expected results in the adult trial. This needs to be addressed so that children don't end up waiting longer than they need to for access to potentially life-saving treatments, or even being told that they can no longer receive a treatment that may have been helping.

When it comes to carrying out clinical trials for treatments for childhood illnesses, cross-border trials are particularly important because these diseases are rare and there often aren't enough patients in one country to make a trial viable. In the past, setting-up a cross-border trial could be extremely difficult as investigators had to apply for authorisation in each country involved. When I led work on the EU's new Clinical Trials Regulation, we made sure this process would become much easier by setting up a single application portal where sponsors can just submit one application for all countries involved. When the law comes into force in 2018, this will make multi-centre trials much easier to carry out and facilitate research into paediatric illnesses.

It's clear that more can be done to improve regulation and give children access to potentially life-saving treatments and I hope the Commission will take these recommendations on board when they review the Paediatric Regulation later this year.

Medicines play an important role in the lives of the citizens



Soledad CABEZÓN RUIZ

MEP (S&D), Member of the ENVI Committee
Rapporteur of the European Parliament own
initiative (INI) report on Access to Medicines.

Talking about medicines in the EU cannot be envisaged without setting it in the context of the public healthcare systems that are characteristic of the EU, highly valued by its citizens, and involving their fundamental right to health. In this regard, we must recognise the paradigm shift that European society is now experiencing as well as the challenges it poses for public health systems, among which we find, in addition to demographic changes, the scientific advances in the field of genetics. The latter have opened up the door to treatments for diseases that had not been addressed so far as well as to personalised therapies or subgroups of patients, which, in turn, initiates reflection on the type of studies necessary to authorise the drug in question, or the access to new technologies, including medicines.

Medicines play an important role in the lives of the citizens, in public health services and the economy. However, the increases in medicine prices, which happened several times over the past years, or the high selling price of those considered innovative mean that pharmaceutical expenditure in the EU now accounts for 17.1% of the total health expenditure and for 1.41% of EU GDP. This is of particular concern as far as the sustainability of the health systems and access inequalities for citizens are concerned. For instance, only 2.4% of Medicaid recipients in the US have received a curative treatment of Hepatitis C

with Sofosbuvir due to the high price of the drug. In the EU no data is available, and only a few Member States have introduced this drug in their portfolio of services with more or fewer restrictions.

In addition to the high prices of medicines, there is also concern about the lack of adaptation to many of the population's needs in commercially less attractive areas, with 13,700 molecules in the pipeline and another 6,900 in the clinical development phase. There is no effective treatment for the so-called neglected diseases or "diseases of the poor", rare diseases or antimicrobial resistance, which causes 700,000 deaths annually due to the lack of an adequate antibiotic, and has brought about the implementation of public incentives, either through public funding of research and/or market exclusivity, among others.

However, the measures put in place so far, such as incentives to develop treatments for rare diseases in the EU, the US or Australia, support the need to consider these challenges as a change broader than the adoption of fragmented measures. And although there has been an increase in the number of treatments for these diseases, there is concern about the high number of this type of designations where more and more oncology medicines are included whose efficiency has not been demonstrated. Moreover, despite public contribution to research, their high prices make them inaccessible to a significant proportion of patients.

In the EU, the number of authorizations for orphan medicines in 2012 amounted to 874; 1,800 molecules are currently under development, with an average growth in spending and using of 13 to 24% and 7 to 17% respectively between 2009 and 2010, and an average price of 150,000 Euro/year for France, Germany, Italy, Spain or the UK. For instance, the 326 orphan medicines that were authorised in the US in the 25 years following the implementation of these incentives currently account for more than half of the annual authorisations, but represent only 5% of the treatments for more than 7,000 rare diseases defined to date.

It should also be pointed out that the use of these regulations for what has come to be called "salami-slicing", – a strategy whereby

an orphan medicine may be authorised for the treatment of indications other than the original ones –, has led these incentives and measures to be questioned and controlled as is the case in Germany where a drug with a sales number of 50,000 is no longer considered as an orphan medicine.

This is at least partly due to the interest of the industry in orphan medicines, given the higher probability of approval of orphan medicines in phase I (25.3%), II (33.3%) and III (65.7%), generating a 1.14 higher return than normal authorisations.

A 68% increased incidence of cancer cases is expected by 2030 compared to 2012, with an estimated 23.6 million new cases annually in Europe. This challenge has to be met taking into account the fact that types of cancer affecting small groups are being genetically identified, and the pharmaceutical sector is pushing for these drugs to be given the designation of orphan medicine yielding a higher return, although in most cases the effectiveness of the treatment has not been proven or life expectancy is increased by a few months.

In short, it is necessary to review the public-private relationship and incentives models in order to provide citizens with an effective, efficient, safe and easily accessible response to 21st century medicine, guaranteeing a return of public investment by looking into patients' needs and ensuring accessibility of treatment through fair prices. As far as public participation in research is concerned there must be transparency about the development and production costs of medicines, research results, and patent rights should be shared. More specifically, a pre-authorisation drug rating system should be set up to fix prices not according to the value from the industry but based on criteria that allow a shared and more balanced benefit between society and companies, and where the evaluation of the added therapeutic value compared with the best possible alternative is crucial, along with other factors such as cost-effectiveness, efficiency or budgetary impact, and authorisations should be subject to clinical results and effectiveness. In short, there is a need for a new type of relationship with the patient at the core of the system.

Investment and incentives in 21st century pharmaceutical research in Europe: the cost of opportunity



Paolo MORGESE

Deerfield Management
Director of Market Access

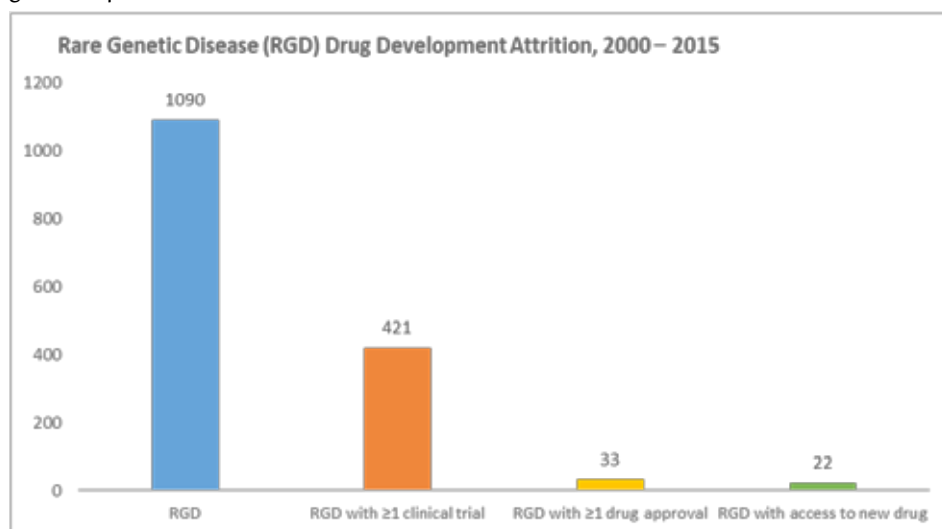
We could say that a financial reward to a successful R&D project is an investment and an investment in healthcare R&D is an opportunity. However, not all investments are successful and opportunities can be missed. And sometimes, one stakeholder's success is another's failure.

Ideally, we would like compelling R&D projects to be cheaply funded, clinical trials to be efficiently and successfully run, and the resulting innovative medicines to be fairly and sustainably priced. Similarly, research institutions would identify unmet needs and conceive innovative ways to solve them. Unfortunately, we do not live in such a perfect world – failures and missed opportunities are frequent, if not the most likely outcomes in this game.

At Deerfield, we have investigated R&D activities for Orphan Medicinal Products (OMPs) for genetic disorders and access to these medicines in the 15 years following the introduction of the European OMP legislation in 2000. Out of 1090 rare genetic diseases, we found 421 diseases (39%) with at least 1 clinical trial documented in the Clinicaltrials.gov database, implying there was no investment in clinical research and possibly no opportunity to invest for ~60% of genetic orphan diseases. On average, 13 clinical trials were completed within the 2000–2015 period for each of the 421 genetic orphan diseases of interest. This

raises the question of how to measure the success of the significant investment behind more than 5000 clinical trials. It is very difficult to say ex-post and obviously much more difficult to say ex-ante. It is possible that all the mentioned studies had good reasons to be done. To determine which were successful, we looked at EU marketing authorizations for medicines indicated for the same set of genetic orphan disorders in the 2000–2015 time period. Only 33 diseases benefited from at least one drug approval, or 3% of the 1090 genetic orphan diseases.

pharmaceutical industry, healthcare policy makers, healthcare professionals, investors, regulators, patient organizations, payers, Health Technology Assessment (HTA) bodies, and many other stakeholders that are part of this admirable R&D ecosystem. Do the above numbers show failures and missed opportunities? Certainly they do. Are they a signal our system is failing? Certainly not – we are actually witnessing one of the most successful periods in the history of healthcare research in finding therapeutic solutions to genetic diseases.



Source: Deerfield Management

Furthermore, only 22 genetic orphan diseases (2% of total) have seen patient access and were marketed in at least one European country during 2000–2015. These figures suggest European patients affected by approximately 98% of genetic orphan diseases did not get access to new OMPs since the implementation of European Orphan Drug regulations. They also suggest that close to 95% of the 5644 clinical trials involving genetic rare disorders reported on Clinicaltrials.gov have not yet benefited European patients – still they may benefit in the future.

How shall we interpret these data? Certainly, they point toward the urgency to find effective and accessible treatments for the majority of people affected by rare genetic diseases or other diseases facing a high unmet need. Arguably, this is the most important common mission for the scientific community,

Against a context of flourishing scientific research, one of the greatest concerns and one of the most recurrent comments in the healthcare policy arena is related to pricing of innovation and affordability. This is often linked to the expected high number of effective new drugs to be launched in the years to come and the concerns over sustainability of public and private payers' budgets.

We are living in an era of enormous opportunities in the healthcare scientific, therapeutic, digital technology and organizational fields. As such, we have the responsibility to find solutions that maximize present and future patients' health. It is time to scale up our rational look at opportunity costs in providing healthcare. This means investing in treatments, other healthcare technologies and infrastructures that provide the most benefit

to patients, while steering clear of those that provide lesser benefit.

Drug price is an important component of the reward that a successful R&D project receives from product revenues once that medicine is on the market. We often hear comments about drug prices considered in absolute terms – for example, whether a price close to €1'000'000 per treatment is morally acceptable. Before commenting on acceptability of some drug prices we should look more closely at the revenues (and costs) generated by these drugs and compare them to the expected benefits. As a counter-example, there may be medicines with a very low price per single treatment that generate very large revenues and profits but that provide only a very limited benefit to the overall population.

Effectively and efficiently rewarding treatments that work well – while divesting from the ones that do not work well enough – is the most important signal that European and global policymakers can give to the industry and investors in fostering innovation in healthcare. This is easy to say but extremely difficult to do. It requires robust methods, skilled researchers, large resources, innovative approaches in collecting real world data and above all, it does not require duplications and inefficiencies in assessing benefits to patients.



Vaccines and public health: how to find the right balance between access, affordability and innovation ?



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Each year in the EU, vaccines protect more than 5 million newborns and about 90 million children against a range of life-threatening and life-changing diseases. In addition, 80 million adults benefit from vaccination against seasonal influenza.

Despite these immense individual, societal and economic benefits, Vaccine Innovation as well as Europe's capacity to fulfil its own vaccine needs are increasingly at risk.

Innovation in vaccines: essential for progress in public health

Vaccine Innovation is essential to progress in the fight against infectious diseases, meaning for Public Health in Europe and worldwide. Vaccine Innovation is necessary to improve existing vaccines and to develop new vaccines to answer unmet medical needs or new needs from emerging infectious diseases like Meningitis or Zika.

Innovation in the vaccines field is also essential to develop manufacturing processes that comply with the stringent European standards, which include:

- Sophisticated mechanisms to generate the antigens that trigger the immune response
- Most effective antigen purification in order to produce a high purity/quality product.
- Robust methods to control every step of the manufacturing process to ensure

that produced vaccines meet the highest quality and safety standards.

Innovation is not only about break-through technologies but also continual improvements in processes and equipment. Indeed, even for simple changes in vaccine manufacturing process, it can take 5 years for full global implementation due to time for approval by all countries.

Two years to manufacture a vaccine – a decade at least to develop a new vaccine

Vaccine manufacturing is complex and challenging. Today, few companies around the world manufacture vaccines for the European or the world population. The entire vaccine manufacturing process, from the virus/bacterial culture to the release of the end product by the referent health authorities, can take more than 2 years, given that up to 70% of the time is dedicated to quality control tests which include re-testing by referent health authorities' laboratory. This long and complex process requires massive investments in industrial capacities and human expertise to meet the highest quality standards essential for vaccines, as well as the European Good Manufacturing Practice guidelines.

Nowadays, a limited number of major manufacturers focus on research and development to improve existing vaccines or develop new ones. The development of new

vaccines requires from 8 to 18 years and a capital investment ranging from \$200 million to \$1 billion or more, including building of manufacturing facilities. These investments can only be undertaken if a company is confident that long-term return can be obtained. With the current pressure on vaccine prices and limited economic incentives, it is becoming increasingly difficult to justify these investments of time, human expertise and capital.

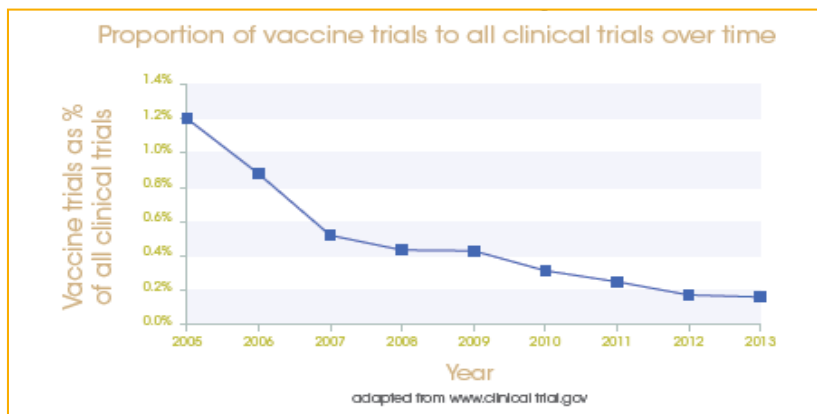
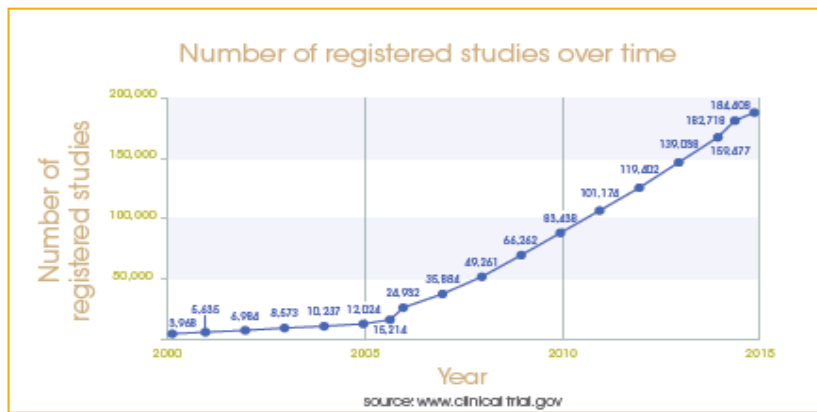
The diminishing number of vaccine manufacturers able to invest in R&D put vaccines innovation at risk

Vaccine R&D processes are complex and require substantial capabilities and colossal investments over a long period, with a high degree of scientific and commercial uncertainty.

Clinical trials are particularly complex and require significant number of participants (several tens thousands of subjects for any pediatric vaccine) due to high safety standards and regulatory requirements

While the total number of all clinical trials (any therapeutic class) has increased over the past ten years, the number of those involving vaccines to prevent infectious diseases has stagnated (Source www.clinicaltrial.gov). Consequently, vaccines represent a decreasing portion of all clinical trials across all therapeutic areas.





Symptoms of an unbalanced vaccines ecosystem

In the vaccines ecosystem, the following signs of imbalance and distress are clearly visible:

- **Vaccine supply capacity has been reduced**
 - Reduced manufacturing capacity means that many vaccines are made by fewer producers, so disruption to any one supplier has a greater impact on people around the world.
 - In 2013, 43% of countries reported experiencing no available stock of at least one vaccine for at least one month.
 - We know that since then, the situation has deteriorated with European countries experiencing difficulties of supply for vaccines included in their national immunization calendar.
- **Vaccine innovation has declined**
 - Due to the reduction of vaccines producers who used to re-invest 15 to 20% of their sales in R&D, vaccines R&D investment has also declined.
 - Vaccines clinical trials represent a decreasing proportion of all studies, which reduces the probability to have successful new vaccines for the future
- **Dis-investment by vaccine producers**

In the objective of better affordability to increase access to vaccination, continuing pressure on vaccine price has finally made vaccine market less viable for producers.

As a consequence, vaccine producers are dis-investing from some or all vaccine areas, notably those with facilities located in Europe.

- Crucell exited from Measles containing Vaccine, Flu and Yellow Fever vaccines.
- Sanofi Pasteur exited from Measles containing Vaccines.
- Novartis exited from the entire vaccine market.
- Baxter exited from the entire vaccine market.

What will the future look like if nothing changes?

There are a number of challenges that may continue to inhibit or stop vaccine innovation:

- Higher regulatory hurdles
- Rising costs of R&D, particularly for new vaccines
- Lower commercial viability, due to continuing pressure on vaccine prices

Pursuing this same direction may lead to further imbalances in the vaccine ecosystem, with further loss of manufacturing capacity and capabilities, notably in Europe, further decline in vaccine innovation that will have consequences for the sustainability of the entire vaccine ecosystem.

In particular, the EU will lose control over its own vaccine supply and over its biodefence. It will become reliant on imported vaccine supplies once having lost their European manufacturing capabilities, in the event of vaccines

shortages, epidemics or even more worryingly, a pandemic or a biological attack, EU Member States will find themselves competing with non-EU countries for available vaccine supply. Inevitably, they risk losing out, as local manufacturers might prioritize their home markets and geopolitical partners.

Conclusion

Public Health decision makers have a responsibility to maintain dialogue with vaccines industry and forge solutions that support stronger vaccine policies and continuous investments through incentives to secure the following:

- Manufacturing capacities & capabilities in the EU for a sustainable supply of high quality vaccines that address the European and world population's needs,
- Timely access to high quality vaccines by lowering the barriers to timely supply through simplification or harmonization of regulatory and release processes
- R&D efforts to ensure that next generation will continue to benefit from innovative vaccines and optimal protection.



Reaping the benefits of healthcare biotechnology in Europe



Nathalie MOLL

Secretary General of EuropaBio

For patients

Healthcare biotechnology has significantly contributed to medical progress for more than three decades. Today, this sector includes bioscience-based enterprises, which are delivering innovative treatments and preventative interventions for the benefit of Europe's citizens and it is estimated that currently 50% of all medicines come from biotech¹. Over 350 million patients around the world are already benefiting from the direct use of biotech medicines², which treat patients for a range of illnesses such as cancers, chronic conditions (e.g. cardiovascular diseases and diabetes) and rare diseases.

By 2020, it is expected that genetic testing will be part of mainstream medical practice, paving the way for increased access to personalised medicine³. Through improved diagnostic techniques using biomarkers and biotech medicines, more targeted treatments are increasingly available for patients and sub-populations of patients suffering from the same disease. Patients are thus increasingly able to access the right treatment at the right time.

Rare diseases, affecting up to 30 million Europeans and their families, are and must remain a key focus of healthcare biotechnology. Since 2000, the EU Orphan Medicinal Products Regulation has enabled the development of an entire sector in Europe. Prior to the Regulation, only eight orphan-like therapies gained approval in Europe, compared to the 122 approved by 2016. The number of orphan drugs approved in Europe has thus increased significantly – allowing biotech medicines to benefit many rare disease sufferers. The Orphan Medicinal Products Regulation has been essential in establishing the predictable and favourable environment necessary for the creation of innovative rare disease treatments.

For society and the economy

The benefits that healthcare biotech brings to patients across Europe goes hand-in-hand with the benefits it brings to Europe on a social and economic level.

It is an extremely diverse sector, making major financial and scientific investments in innovation across the EU. There are over 3000 companies in Europe, ranging from large

companies with annual R&D expenditures of 1-4 billion, to medium-sized as well as much smaller enterprises, with fewer than 10 employees running on grant-based incomes alone.⁴

Healthcare biotech products also enable individuals to stay healthy and active for longer, which reduces the burden placed upon national healthcare services; with hospital stays replaced by medication and in some cases through prevention. In turn, this contributes to a healthy labour force with less absenteeism and higher productivity. For example, over the last twenty years, biological medicines have reduced the progression of multiple sclerosis; an autoimmune disease, which is a leading cause of disability in adults. In Europe, between 500,000 and 700,000 people are living with this disease that often exhibits peaks of activity and sometimes, long periods of dormancy. It has been estimated that the costs of Multiple Sclerosis across

⁴ OECD (updated October 2016) Key Biotechnology Indicators see <http://www.oecd.org/sti/inno/keybiotechnologyindicators.htm>



¹ EY and EuropaBio (2014) [Biotechnology in Europe](#)

² Charles River Associates (CRA)(2014) [Valuing Healthcare Biotech in Europe](#)

³ Deloitte (2017) Global Life Sciences Sector Outlook 2017, p.14

Europe were in excess of €15bn, with lost productivity accounting for 36% of these costs⁵.

Furthermore, the healthcare biotech industry creates hundreds of thousands of high quality permanent jobs in Europe through all stages of the biotech value chain. It also contributes to the EU economy through trade via the sale of innovative products from Europe to leading markets, such as the US and Japan and by meeting the growing demand of middle-income countries. It has been estimated that the healthcare biotech industry in Europe is manufacturing 79% of all vaccines and 26% of all biologics worldwide⁶.

The challenge

Healthcare biotechnology is undergoing rapid transition demonstrated by radical advances in its science base, increasing regulation and competition due to the globalisation of markets. This presents challenges to the sector in Europe right along the value chain: from competitiveness to attract start-ups and clinical trials, to maintaining a vibrant manufacturing sector, a robust intellectual property regime, and continued smart spending from national governments.

⁵ Knülle et al (2011) From disability to ability at work Successful case management approaches in multiple sclerosis, Swiss Multiple Sclerosis Society (also see <http://www.emsp.org/wp-content/uploads/2016/01/MS-employment-Lit-Rew1.pdf>)

⁶ Charles River Associates (CRA)(2014) Valuing Healthcare Biotech in Europe

Moving forward

Industry must work to find new solutions to old and new healthcare and economic problems. There is a growing need for industry to highlight the benefits of healthcare biotech to achieve the support it needs. Through national, regional, and European initiatives such as [European Biotech Week](#), industry can explain its importance to society and the European economy.

EU policy makers must simultaneously prioritise healthcare and have an enduring vision for modern healthcare, with focus on making Europe a predictable and attractive location for biosciences. Standing by these ambitions is important for the creation of a holistic healthcare system in Europe. Continued support in healthcare biotechnology will ensure that new products keep on being developed. The outcome of this will be a healthier and more productive society, whilst creating high quality jobs and adding much needed value to the European economy.

We look forward to discussing new options for maintaining Europe's place as a global leader in health bioscience. What is at stake is not only patients' wellbeing, but also the full range of societal benefits deriving from a healthier population and the viability of the European industry. Healthcare biotechnology must continue to play a central role in Europe's agenda if we are to ensure Europe's patients, society and the economy can continue to reap its benefits.



Delivering next generation of immuno-oncology therapies in managing cancer



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Boosting the immune response, particularly by administering cytokines, to kill cancer is a concept that has been examined in the clinic several decades ago. However, clinical benefit was dismal and arrived at the expense of considerable toxicity. Yet, with long term observation particularly in kidney cancer, it was interesting to find that some of these responses were durable with about 5-10%¹ of the patients achieving long term remissions. This indicated that perhaps with better understanding of the cancer immune escape mechanisms, more refined strategies could be identified.

Over the last decade, remarkable progress has been made in understanding the key role of the immune system in controlling and killing of cancer. Among the key milestones was the recognition that there are signals responsible for activating the immune system to elicit an anti-tumor response. These signals are often disrupted in cancer by the so called “checkpoints”. This has led to the development of several agents referred to as “checkpoint inhibitors” that are currently revolutionizing the way malignant tumors are treated and hold a huge potential of changing the landscape of cancer management for many years to come.

Nowadays, several checkpoint inhibitors are offered to patients in routine clinical practice following a series of clinical trials that demonstrated remarkable benefit in the treatment of cancer. The first results were reported for the CTLA4 inhibitor, ipilimumab, demonstrating an improvement of overall survival over single agent chemotherapy in malignant melanoma², which is an aggressive form of skin cancer. However, this was at the expense of important toxicity, with more than 50% of patients developing severe side effects. Few years later, PD1/PDL1 inhibitors emerged as a more effective strategy associated with less toxicity. This was clearly demonstrated in the head-to-head comparison of the anti-PD1 monoclonal antibody pembrolizumab with ipilimumab in melanoma³, with the former showing significantly better safety profile, response rate and survival. Importantly, disease responses were long lasting in an important fraction of patients, an observation which was rarely observed with previous standard therapies.

Non-small cell lung cancer is another disease that has been completely transformed by immuno-oncology agents. In previously treated patients, the PD1 inhibitors

nivolumab and pembrolizumab were shown to be superior to standard chemotherapy⁴. In newly diagnosed patients, pembrolizumab was also shown to significantly improve patient outcomes in patients with high PDL1 expression ($\geq 50\%$) and is currently considered a new standard-of-care.

Anti-PD1 antibodies were also explored in other solid tumors and are currently approved in kidney cancer, and head and neck cancers following impressive results. On the other hand, the other class; PDL1 inhibitors, are increasingly being introduced after the approval of durvalumab in previously treated bladder cancer and atezolizumab in previously treated non-small cell lung cancer. Both classes, the PD1 and PDL1 inhibitors are being explored in virtually all tumor types in various indications and are currently placed at the forefront not only of immuno-oncology agents but also of cancer treatment in general.

Despite the unprecedented benefit and also the hype that is associated with anti-PD1/PDL1 agents, they remain short of curing patients with more than 50% of patients deriving no benefit. This has promoted to exploring novel strategies. This ranges from combination strategies of different classes of checkpoint inhibitors, to agents that act on specific receptors that modulate the immune response against cancer, or other strategies that improve the recognition of cancer by the immune system or boost the immune response. Several of those approaches have shown promising preliminary data and advancing well in clinical development as will be discussed briefly in the remainder of this article.

Combination of an anti-PD1 and anti-CTLA4 was a logical first step given the important activity observed by each of them as single agents⁵. This strategy was shown to be more effective than anti-PD1 therapy alone in melanoma yet at the expense of considerable toxicity. However, the improved activity has provided an important signal that a dual

1 Amin A & White RL. Interleukin-2 in renal cell carcinoma: a has-been or a still-viable option. *Journal of Kidney cancer and NHL* 2014

2 F. Stephen Hodi et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. *N Engl J Med* 2010; 363:711-723

3 Robert C. et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med*. 2015 Jun 25;372(26):2521-32

4 Pankit Vachhani and Hongbin Chen. Spotlight on pembrolizumab in non-small cell lung cancer: the evidence to date. *Onco Targets Ther*. 2016; 9: 5855–5866

5 Larkin et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* 2015; 373:23-34

combination of two immuno-oncology agents is worthy consideration. Preclinical experiments have shown that combination with other T cell checkpoint inhibitors like LAG3 and TIM-3 is synergistic and this is currently being explored in clinical trials.

A combination approach with checkpoint inhibitors that targets receptors expressed on other immune cells like natural killer (NK) cells (unlike PD1 inhibitors that work on T cells) represents another novel concept. In a phase I/II trial in patients with advanced head and neck cancer, the combination of lirilumab – a checkpoint inhibitor working primarily on NK cells – and the anti-PD1 nivolumab was associated with a response rate of 24%, complete response of 10% and one year survival exceeding 50%⁶. These early results compares favorably to historical data with nivolumab alone. Importantly, this does not arrive at the expense of considerable toxicity with a safety profile comparable to what observed previously with nivolumab alone. This strategy is currently being further explored. Another novel combination is the addition of an IDO1 inhibitor; epacadostat to the anti-PD1; pembrolizumab. IDO is an enzyme responsible for allowing tumor cells to escape recognition by the immune system. Results from an early clinical trial across several tumors showed an overall response rate of 57% including two complete responses⁷. Further studies with this combination are currently ongoing too.

Apart from targeting checkpoint receptors, other strategies targeting the immune system repertoire have been described as well. Novel antibodies acting on receptors expressed on the T/NK cells have been recently tested in the clinic. One example is IPH4102; a monoclonal antibody directed against KIR3DL2, which is a receptor expressed on several types of T-cell lymphoma. Early clinical data was presented in late 2016 showing promising activity with durable responses observed in patients with heavily pretreated cutaneous T cell lymphomas⁸.

Another appealing approach is the so-called bispecific T-cell engager (BiTE) antibody

technology, which stimulate the immune system (mainly T immune cells) to initiate a response against cancer. One example is blinatumomab, which is currently approved in managing advanced acute leukemia after showing an impressive complete response in nearly 40% of patients⁹. Some challenges remain though with this strategy including the high risk of developing seizures, which require precautionary preventive measures.

Adoptive cell transfer is another strategy that involves the isolation of tumor infiltrating immune cells (lymphocytes) – which represents the attempt of the body to fight tumor growth – growing them outside the body and then introducing them again to the patient. Early clinical experience in melanoma has shown high and durable complete responses¹⁰. Promising results were observed in other solid and hematological cancers too. While early data are promising, the challenge remains in the considerable toxicity of this approach in addition to its potential clinical application on a wide scale as isolation and reintroduction of T cells is rather complex and requires a dedicated setup.

In conclusion, we are currently witnessing just the beginning of a very exciting era of immuno-oncology agents in managing cancer. Immune checkpoint inhibitors particularly anti-PD1/PDL1 monoclonal antibody represent the tip of the iceberg and it would not be too long until some of the other novel agents and strategies become part of the repertoire available to manage and hopefully cure cancer patients in daily clinical practice.



Jean Marie Huron

6 Rom Leidner et al. Preliminary efficacy from a phase 1/2 study of the natural killer cell-targeted antibody, lirilumab in combination with nivolumab in squamous cell carcinoma of the head and neck. Late-breaking abstract presentation at SITC 2016 (abstract 456)

7 Gangadhar TC et al. Preliminary results from a phase I/II study of epacadostat (incb024360) in combination with pembrolizumab in patients with selected advanced cancers. *Journal of Immunotherapy of Cancer* 2015 3 (Suppl 2):O7

8 M. Bagot et al. First-in-Human, Multicenter Phase I Study of IPH4102, First-in-Class Humanized Anti-KIR3DL2 Monoclonal Antibody, in Relapsed/refractory Cutaneous T-Cell Lymphomas: Preliminary Safety, Exploratory and Clinical Activity Results. Abstract 1826 ASH 2016

9 Topp M., Gokbuget N., Stein A., Zugmaier G., O'Brien S., Bargou R., et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol* 2015 16: 57–66

10 Lu YC et al. Efficient identification of mutated cancer antigens recognized by T cells associated with durable tumor regressions. *Clin Cancer Res* 2014

“European Reference Networks: a way forward in the treatment of rare diseases”



Françoise GROSSETETE

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The Regulation (EC) 141/2000 on orphan medicinal products is probably one of the pieces of legislation I am the most proud of, as it has proved to be a crucial milestone in incentivizing research and development in the area of rare diseases. It has been further completed by another piece of legislation I had the honour of carrying through Parliament: the Directive on Patients' Rights in Cross-border Healthcare. I believe there is a critical link between those two pieces of legislation.

Indeed, one the key provision of the Cross-border care Directive was the establishment of European Reference Networks (ERNs) for rare diseases. It all started from a simple consideration: rare diseases having a very low prevalence, they are often misdiagnosed or diagnosed very late, information is scarce (both for patients and health professionals) and treatments are not always available in the patient's home country, as access barriers remain.

Considering this situation, the European scale appeared to be the right one to improve the treatment and organise the fight against rare diseases. We started to dream of a system, which would allow Member States to better share their information and data on the 6 000 rare diseases existing today, to put in common their resources, and to make it possible for patients to be treated where the best expertise

is available. Because of the low prevalence of rare diseases, knowledge sharing has never made more sense than in this therapeutic area.

That is exactly the reason why European Reference Networks were created. ERN create a clear governance structure for knowledge sharing and care coordination across the EU, ensuring clinicians have the most recent and expert knowledge possible, which in turns allow them to make better informed decisions on how to adapt treatment and care pathways.

As a result, both health professionals and patients will have easier access to expertise on rare diseases beyond their national borders. Patients will no longer find themselves isolated and vulnerable. I am proud to say that France is a leading country in this respect with an important number of centers of reference, whose added value has highly contributed to improve the identification of those patients still waiting for a diagnosis and who often feel isolated and unprepared to face a fight against their disease. However, not all countries are keeping up at the same pace and it is our duty, as European policy-makers, to address the disparities among European countries by fostering the setting up of European Reference Networks (ERNs).

Mid-December 2016, the Board of Member States of ERNs approved all 23 ERN proposals submitted under the first wave of applications and the 24th network was approved under the second wave on 16th February 2017. This a true progress and a great step forward. Member States encouraged the participation of their leading centers for expertise, making those calls and undeniable success.

Still, I am afraid that the fragmented and piecemeal nature of the networks could hamper its effectiveness. In this respect, more needs to be done to ensure a swift implementation of the Directive 2011/24/EU on the application of patients' rights in cross-border healthcare. I would also like to see a better implementation, and a better monitoring, of the recommendations of the European Union Committee of Experts on Rare Diseases (EUCERD) on 'quality criteria for centers of expertise for rare diseases in Member States', published in 2011.

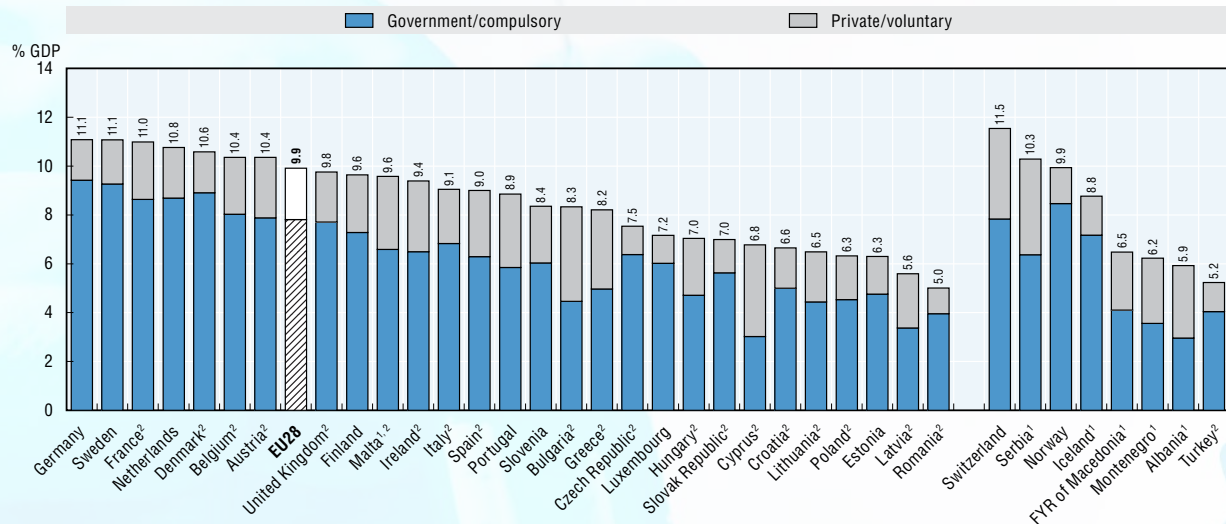
Patients suffering from rare diseases are often facing life-threatening conditions and severe pain. Timing is crucial for them and they should not wait years before being correctly diagnosed. They deserve a timely and appropriate diagnosis today. They deserve equitable conditions of access to care. They deserve to have their voice heard through their patients' associations. And this, disrespectfully from their country of residence.

This initiative shows an area where a European cooperation can really be beneficial, make a concrete difference in citizens' lives and go beyond the diversities of healthcare systems. Many patients are still waiting for a diagnosis or are neither yet aware of their conditions nor that a therapy could be available for them. The European Reference Networks can bring added value and be critical in this respect, by bridging the gap among the inequities at national level. Patients' interests have to come first and it is the responsibility of the European governments to make a difference for them.





Health expenditure as a share of GDP, 2015 (or nearest year)



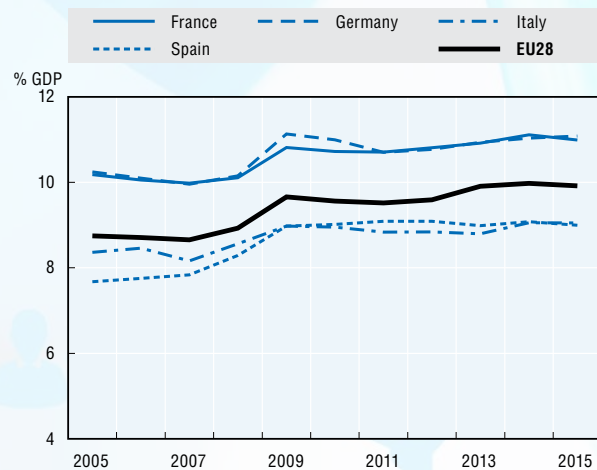
1. Includes investments.

2. OECD estimate.

Source: OECD Health Statistics 2016; Eurostat Database; WHO, Global Health Expenditure Database.

StatLink <http://dx.doi.org/10.1787/888933429258>

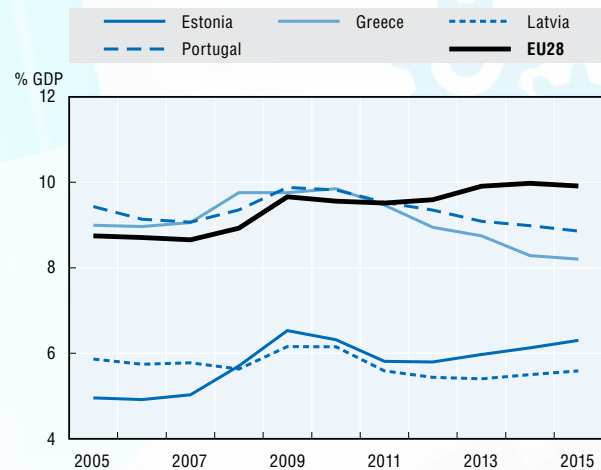
Health expenditure as a share of GDP, selected European countries, 2005-15



Source: OECD Health Statistics 2016; Eurostat Database.

StatLink <http://dx.doi.org/10.1787/888933429269>

Health expenditure as a share of GDP, selected European countries, 2005-15



Source: OECD Health Statistics 2016; Eurostat Database.

StatLink <http://dx.doi.org/10.1787/888933429274>

Open Innovation for a Strong R&D network



Lieve WIERINCK

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The pharmaceutical industry is inherently innovative, with a very strong focus on research and development. For a long time the outcome of these in-house R&D processes were great. Truly innovative medicines, medical breakthrough and real societal progress were to a large extent thanks to this industry. However, we have seen that over the past 40 years the R&D costs have risen significantly, with a yearly inflation-adjusted increase of costs of approximately 7-10%. This meant that in 2013, it cost on average 2 billion euro to develop a marketable medicine, taking 12-13 years to accomplish this. At the same time, with this elevated cost and long R&D process, we see that the yearly amount of new authorized medicines by the European Medicines Agency (EMA) has only slightly increased over the last ten years. Moreover, many stakeholders claim that this innovation is incremental, representing only very limited added value. According to these voices in the European policy arena, the era of breakthrough innovation is behind us, and claim these so-called 'me-too' drugs have little benefit for the patient. Now the question that we should all - industry, researchers, patient organisation and policy makers - ask ourselves is how we can overcome the problem of a seemingly underperforming pipeline. Many industry observers have also commented that the many takeovers and consolidation within the sector have not led to the paradigm shift in R&D which we might need.

That's the reason I want to make the point for open innovation. This is a way of promoting both internal and external sources of innovation. Now, of course this idea sounds counter intuitive in an industry which is born and bred in a very strict IP framework, the life and blood of its business model. Why should companies work together and share information, amongst each other and with research institutions and other actors in their innovation ecosystems? A first reason would be that, according to a 2010 Morgan Stanley report, the pharmaceutical industry does not generate sufficient income to sustain large internal R&D divisions, let alone cover for the cost of failure. I believe the future effective pharmaceutical companies will be in the centre of an ecosystem with other companies, SME's and research institutions, all with their own knowledge and expertise. Being able to manage and navigate this complex setting of organisations will be crucial for future sustained competitive advantage.

In the recent years we have already seen a move to a more collaborative approach to solving scientific bottlenecks, through the Innovative Medicines Initiative (IMI). Although IMI is limited to what is called pre-competitive collaboration, other initiatives have been developed. One of them is the voluntary exchange of clinical trial data with academic researchers, as laid out in the "Principles for Responsible Clinical Trial Data Sharing", agreed by EFPIA/PhRMA. This text sets out that their member companies will - on request - share data with academic researchers, in order to make further progress in the scientific domain. This is another important indication that we are moving into a situation where data sharing will be considered beneficial, and not a liability for future profitability.

Sharing these data is certainly a step forward in developing science, but still does not solve the issue of the slowdown in innovation from within the pharma companies themselves. The last years however, they too have made a move into a more open method of innovation. In this case, open collaborations with research institutions and academia provide them with the input they need. Pharmaceutical companies need to harness knowledge both within and outside their organisation. This requires many changes, such as a change in

company culture or aligning open innovation with company strategy. Open innovation has already been common for many years in some of the most creative and innovative sectors. We also see that the Commission is adopting a more open approach to R&D, with its "Open innovation, open science, open to the world" communication, amongst others. Making research results more easily accessible helps developing a more efficient science, innovation, both in public and private sectors. This kind of collaboration can take on many forms: licensing agreements, investing in a start-up testing new therapeutic concepts or simply working together with the other actors in the healthcare ecosystem. We already see clear examples of this approach: Lilly with its Open Innovation Drug Discovery (OIDD), or other co-operation initiatives such as the oncology immunotherapy one with Merck, Amgen, Pfizer and Incyte. I am convinced that we will see more of these types of collaboration come up in the years to come. As policymakers, we should have a clear understanding of what this process entails, and lead by example. Horizon 2020 and IMI are ideal instruments to show the added value of co-operation. Or as the African proverb says: "if you want to go fast, go alone. If you want to go far, go together".

A tale of two horizons – patient access in the age of innovation



Thomas ALLVIN

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Go to any medical congress, read any medical journal, and you will face an avalanche of scientific discoveries faster than the human mind can progress. New immunotherapies activating the patients own immune system for combating cancer, monoclonal antibodies for treating early stage Type 1 diabetes, medicines targeting autoimmune disorders such as MS and arthritis, and very advanced cell- and gene therapies, replacing or repairing faulty cells and even genes in the human body, to name a few examples. Researchers in academia and industry is bit by bit cracking the code of disease after disease, painting a promising picture for the future of human health and wellbeing in the 21st century.

At the same time, the outlook can be quite different at the other end of the pipeline, the one often called “patient access”, but most users of healthcare probably would refer to as “getting the best available treatment when I’ve fallen ill”. Just like you could spend every day shifting through news of fantastic medical progress, few days go by without news of a drug failing to meet its clinical endpoints in phase 3 despite earlier promise, or of an approved drug being rejected by a HTA body, or simply not being reimbursed or put in use by a country or region, either due to general slow uptake of innovation in clinical practice or on the account of being deemed too expensive. Or it

will be reimbursed, eventually, but first put on a waiting list.

All this creates delays for patients in getting access to the latest medical innovations. And it creates unequal access – some patients get faster access to new medicines than others, often depending on where you live, but sometimes also depending on how much you can pay yourself.

Although there are many and sometimes complex reasons for new medicines not reaching patients as fast as they should, two particular situations is featured more often in the debate. One is when decision-makers and clinicians have doubts about the exact effectiveness of a new drug in clinical practice. The other is when a clearly groundbreaking drug gets disruptive for the system. Let’s take these situations in turn.

A quite common barrier to access is lack of consensus on the effectiveness of a drug in clinical practice. We see it often for innovative cancer treatments, in situations where the clinical trial data show effectiveness for a certain period of time, but no one knows exactly how sustainable the treatment effect is over time. The advent of stratified medicine, targeting smaller patient populations, naturally lead to more of these problems. There is however solutions that can provide the payers with the certainty they need and at the same time give patients access to new drugs. “Managed entry agreements” can be used to condition the reimbursement of a drug with a monitoring programme where data is continuously collected from the patients to confirm the long-term value of the treatment. Increasingly, the reimbursement itself is adjusted to the real-world result of the drug, a model that requires systematic data collection but can square the circle of guaranteeing patients and payers true value for money also when using drugs that are relatively untested in clinical practice.

The other is when a new therapy completely changes the paradigm, but at a high upfront cost for the system. The new Hepatitis C treatments are a case in point – no one doubt their fantastic results, or even that they are cost-effective since they save the system – and the patients – from the long-term burden of

treatment, including the need for liver transplants. But a small or medium-sized budget holder in a region or a hospital who is used to handle “business as usual” doesn’t have the tools to handle a big upfront cost today, even if it means completely curing patients from a harrowing disease and saving a lot of money down the line. And if you think that Hepatitis C was a black swan event, think again. The new gene and cell therapies that are currently working their way through the pipelines of the industry will have a similar effect, although for fewer patients. Gene therapies could for example dramatically change the life for patients suffering from hemophilia, substantially reducing the need for continuous treatment and risks for hemorrhages. But replacing a life-time supply of medicines with one, highly advanced and high-cost intervention at one point in time create very similar challenges for the system in terms of resource allocation. Here new solutions are needed for the financing of healthcare. It’s not really rocket science – financial institutions are used to deal with big upfront investments that will pay off over time – but it requires that health policymakers and healthcare managers, together with the industry, are ready to find new solutions when the old are no longer fit for purpose.

And sometimes – let’s face it – should countries simply increase the budget they spend on healthcare, as the European Commission recently recognized after having assessed the healthcare systems of some countries in the context of the European Semester cycle.

So there are ways of bringing new, innovative medicines to patients without unnecessary delay. What is required is horizon scanning, to understand what therapies are coming down the pipeline in the near future, planning to prepare all actors in the healthcare systems to introduce these innovations, and sometimes a bit of creativity and out-of-the-box thinking. In all of these steps, the industry wants to work together with all stakeholders – from patients to clinicians and payers – to find the solutions that transform the promise of innovation into a healthier future.

The Innovative Medicines Initiative – putting patients at the centre



Pierre MEULIEN

IMI Executive Director

Patients increasingly want and expect to be involved in all aspects of medical research and drug development. Since its creation, IMI has worked hard to integrate patients into its projects and activities, but I am convinced that we can and should do more. Not only because patients want it, but because IMI needs it; put simply, if we at IMI want to develop an open innovation ecosystem in health research and achieve our own ambitious goals, greater and more structured patient input will be essential.

There are a number of changes afoot in the medical research and drug development world that are forcing stakeholders to rethink their ways of working. These include advances in science and technology, especially the rise of digital health technologies; epidemiological drivers, such as how best to prepare for and respond to outbreaks of infectious diseases; and the role of patients in research. In this article, I want to focus on the last point – the growing importance of engaging actively with patients in all aspects of medical research and drug development.

IMI and patients – a long-standing partnership

Patients have been involved in IMI's activities from the beginning, as members of committees and evaluation panels and as expert speakers at events, for example. We have also

held a number of workshops specifically targeting patients to gather their feedback and views on our work. Patient involvement is also integrated into discussions on things like the development of new projects.

Patients are also directly involved in many IMI projects. Some projects focus specifically on patient involvement in research; the goal here is to ensure that patient involvement is meaningful and effective (and not tokenistic). The flagship project here is EUPATI, which has just finished. Led by patients, the project set out to provide patients and patient advocates with the skills and knowledge needed to actively participate in and contribute to medicines development at all levels. The project ran high-level 'expert' courses for close on 100 patients and advocates in the details and jargon of the process of medical research and drug development, covering subjects such as medicines regulation, clinical trials, statistics, evidence, and ethics. I met the course graduates when they received their certificates and was inspired by the way they are already applying their new-found skills and knowledge in their daily activities as patient advocates in a wide range of settings.

EUPATI also created a multilingual website, www.eupati.eu, which is packed with information on drug development so that patients across Europe and beyond can learn about this complex process. The course also includes

materials that can be easily turned into training courses for different patient communities in different countries.

The success of EUPATI is further demonstrated by the fact that the project has secured follow on funding from outside IMI to continue running the expert course after the IMI funding period has finished.

Meanwhile IMI recently launched a new project, PREFER, which aims to assess when and how patient preferences on benefits and risks should be incorporated into decisions on medicinal products. While there is broad agreement that patient preferences are very valuable, there is little guidance on conducting and using such studies. The goal of PREFER is to provide a set of systematic methodologies and recommendations to assess, engage and include patient perspectives during the development, approval, and post-approval of new therapies. PREFER brings together experts from academic research institutions, pharmaceutical companies, patient organisations, a health technology assessment body, and SMEs. In addition the consortium has set up stakeholder advisory groups to work closely with patients, regulators, health technology assessment (HTA) bodies and payers, to ensure that recommendations are evidence based, relevant and useful.

Finally, at the end of 2016 we included a topic on patient perspectives in research in our



most recent Call for proposals (IMI2 – Call 10). The goal of this topic is to provide a framework and guidance for all stakeholders on the best ways to meaningfully engage patients at different stages of the medicines lifecycle.

Many of IMI's scientific projects also have strong patient involvement. For example, patients played a big role in the severe asthma project U-BIOPRED; as well as participating in the project's scientific and ethics boards, patients helped in many aspects of the project, including fine-tuning research protocols and driving patient recruitment. The project partners drew on their experiences to produce a handbook on successful patient participation in research.

A number of IMI's Alzheimer's projects benefit from the involvement of the pan-European patient group Alzheimer Europe. Among other things, the projects benefit from Alzheimer Europe's communications channels and relationships with key policy makers and opinion leaders throughout Europe.

Diabetes charity and patient organisation JDRF joined IMI as an Associated Partner, meaning that it does not receive any funding, but contributes its own resources to the projects it is involved in. They cite IMI's commitment to putting patients at the centre as one of their reasons for getting involved in IMI.

'Nothing about us without us' and other reasons to work with patients

Our experience of working with patients at IMI has demonstrated a number of things. Firstly, patients increasingly want and expect to be actively involved in all aspects of research – 'nothing about us without us'. Secondly, thanks to projects like EUPATI, and patients' own efforts, there are more and more patients (and carers and advocates) who have the knowledge and skills to participate fully and actively in medical research and drug development projects, as fellow experts alongside scientists and regulators, for example.

Finally, there is growing recognition in the research community that bringing patients on board is beneficial for projects. Patients have intimate knowledge, from their own experience and that of their networks, of the day-to-day reality of living with the disease under study. This perspective can prove valuable when identifying research priorities, when designing clinical studies (to ensure they are patient-friendly), and when assessing benefits and risks.

Patient groups can also aid in communication, as they are often skilled at turning scientific results into lay language and have good contacts and channels that help the project get its messages across to the general public, press and policy makers.

We have also found that patients bring a lot of energy and drive to projects, and when challenges arise, patients help other partners to keep the project on track.

Patients are key to IMI's success

For us at IMI, all of this raises the question of how we, as a research-funding body, can ensure that we continue to practice what we preach and do as much as we can to get patients involved in our activities. We already do a lot, but I believe that we can and must do more. Patient engagement throughout the innovation life cycle is indeed an evolutionary process. We have gone from a 'tokenism' approach (remember to include a patient so that we can tick the box!) to one where the quality of the project deliverables is dependent on patient input. We now need to get to the next level where patients will be co-developing strategies, programmes and projects with policy makers, funders and actors in the complex environment of healthcare innovation.

Our goals, as set out in the IMI2 legislation, are extremely ambitious and I am convinced that greater patient input will be essential if we are to achieve those goals and help to create a truly open, collaborative environment for medical research and innovation in Europe.

With this in mind, at IMI we are currently exploring more structured ways of gaining patient input on our activities. One idea here would be to create a dedicated patient platform that could provide advice and ideas to the Programme Office and IMI's various governance bodies. Such a committee would also form a strong link between IMI and the wider patient community in Europe and beyond.

Whatever form IMI's future patient engagement activities take, I hope that the patient community will continue to challenge us and give us ideas so that our projects will continue to meet their needs as well as the needs of our wider stakeholder community.

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. 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. 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.

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“Ensuring equal access and catering to the needs of patients in smaller EU Member States”



Andrey KOVATCHEV

MEP (EPP Group), Substitute of the
ENVI Committee - EP Presidency Member
(Quaestor)

Health inequalities are one of the important, yet often overlooked, challenges confronting the European Union. The reality that patients' needs are not equally addressed across the EU due to limited access is one of the main causes for the existing health disparities. While ensuring equitable access to quality healthcare is in no way a challenge unique to smaller EU Member States with limited resources, they are often the ones who find it most difficult to cope with them.

Evidence for this statement provides the example of rare diseases. These are diseases affecting fewer than five in 10 000 people. Currently between 6-8% of the EU population suffers from one of the 6000 to 8000 known rare diseases. Smaller countries find it very difficult to provide the small number of patients affected by one of these rare conditions with the much needed specialised care, because of insufficient resources and lack of relevant expertise. To tackle this problem and ensure access for European patients to the best available diagnosis and treatment, it is therefore crucial to enhance cooperation between Member States and pool the available knowledge through the establishment of networks of experts. The Directive on the application of patients' rights in cross border healthcare adopted in 2011 gave impetus to the development of the so-called European Reference Networks (ERNs) and in March, we

will finally see the official launch of the first ERNs. If properly implemented, they have the potential to dramatically improve the access of patients suffering from rare diseases to effective and high-quality healthcare.

When we talk about access, we need to recognise that it is a multi-dimensional issue, which is the result of complex interaction between various factors. Ensuring that quality healthcare services are accessible for all EU citizens in an equitable manner is a process that cuts across multiple actors and institutions. The inclusion of the various stakeholders is therefore of paramount importance in order to develop sustainable solutions to the problem. However, this is easier said than done. Collaboration means uniting efforts towards the same goal, yet many stakeholders are reluctant to leave their professional silos. A major step forward was made in this regard with the establishment of the Patient Access Partnership (PACT) - a patient-led multi-stakeholder platform bringing together patients, the medical and public health community, industry as well as the European and national policy-makers and institutions. Still in its formative years, PACT has achieved significant progress in establishing access to healthcare at the centre of the political debate at European regional and national level. This demonstrates that problems can be better addressed when all stakeholders are involved in the process.

At the same time, there has been a growing interest from the European Parliament in the topic of access to healthcare. A report on “EU options for improving access to medicines” was recently adopted by the ENVI committee and will be voted during the March mini-plenary session. Access to medicines is one of the fundamental aspects of accessible healthcare, because medicines are one of the main pillars of the health system and not mere objects of trade. Overwhelming evidence suggests that affordable innovative medicines, which promise to cure or ease the burden of a disease, constitute a main component of accessibility, especially for patients with a chronic condition. Taken individually, smaller and low income countries have less power to negotiate prices, which can make medicines in such Member States less affordable. In recent years, we have seen the emergence

of several regional cooperation initiatives to jointly negotiate drug prices, for example between the Benelux countries and Austria, and more recently between Romania and Bulgaria. It is worth acknowledging that the pharmaceutical industry is important as an indispensable source of medical innovation. The biggest pharmaceutical companies are very well structured multinational players, which benefit from the economies of scale in research and manufacturing, thus increasing efficiency and decreasing costs. However, this suggests that negotiations take place in a context of information asymmetry between globally scaled companies and individual Member States. While there are reasons for the variations in medicine prices between Member States, such as different economic conditions, there is great potential for countries with similar socio-economic profiles to reinforce their negotiation capacities through closer cooperation in price negotiations.

Another area where stronger cooperation at the European level promises to improve access for patients in smaller Member States is broadly referred to as Health Technology Assessment (HTA). Unfortunately, today innovation does not reach all Member States with the same speed. Medicines available in one country may not be available in another, thus putting some patients at a disadvantage. More specifically, the continuous harmonization of the clinical component of HTA, which focuses on the assessment of the medical or therapeutic added value of a health technology compared to existing alternatives, can help better inform the decisions of national healthcare decision-makers and contribute to the equity of access to healthcare throughout the EU. Given their size and limited resources, many smaller Member States have not yet developed the comprehensive infrastructure needed to conduct HTAs in a consistent manner and can benefit from greater European collaboration.

Access to Quality Care: The Patients' View



Nicola BEDLINGTON

EPF Secretary General

The European Patients' Forum (EPF) is an umbrella organisation that works with patients' groups in public health and health advocacy across Europe. Our 67 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.

Access to quality, patient-centred and sustainable healthcare is a long-standing priority for the European Patients' Forum (EPF) and its membership, and is at the heart of the vision of the organisation. In January 2017, EPF launched a one-year flagship campaign on access to healthcare, under the tagline 'Universal Access to Healthcare for All by 2030'. The campaign is an opportunity to raise awareness about the barriers patients face in accessing healthcare, and to build on current political momentum, including the UN sustainable development goals for health, to foster more EU cooperation on access to healthcare.

The UN Sustainable Development Goal for Health & Well-Being

The sustainable development goals for health and wellbeing aim to ensure healthy lives and to promote the well-being for all at all ages. From the patients' perspective, a key opportunity within the health goals is to

achieve universal health coverage by 2030. We believe this specific goal is essential to achieve other health and wellbeing goals such as reducing premature mortality from communicable and non-communicable diseases.

EPF Definition of Access

Further to a wide consultation, EPF developed a definition of access to healthcare which encompasses the key dimensions to ensure equitable access to high quality healthcare from the perspective of patients with chronic conditions.¹

These five main dimensions are as follow:

- Availability – whether a healthcare service or product is available in the healthcare system of a country;
- Affordability – whether seeking healthcare causes financial hardship to patients;
- Accessibility – whether there are barriers, other than financial (e.g. waiting lists, geographical barriers...), that stop patients from accessing healthcare;
- Adequacy – the quality of healthcare and involvement of patients in shared decision-making with their healthcare professionals;
- Appropriateness – whether healthcare meets the need of different groups in the population.

A core dimension of our definition of access is adequacy, which refers to the quality of care. Healthcare should be constantly adapted to the needs of patients. To this end, ongoing dialogue between individual patients and their healthcare team is essential. It requires patient involvement at individual level through shared decision-making and adequate mechanisms to capture patients' feedback and at collective level in health policy decision making.

A Survey on Access from the Patients' Perspective

In late 2016, the European Patients' Forum launched an extensive [survey](http://www.eu-patient.eu/globalassets/policy/access/epf_position_defining_and_measuring_access_010316.pdf) on access to healthcare from the perspective of the patients. The objective of this questionnaire was to gather knowledge on the experience of patients with chronic and long term conditions and family carers on access to

healthcare across the European Union and across conditions.

Over 3 months, 395 respondents from the 28 EU Member States took the survey and shared their experience of access to care. After careful analysis, the results are now publicly available. Let's zoom in on the answers related to quality of care and the patient-healthcare professional dialogue.

Quality of Care Does not Always Correspond to Standards

When asked if they receive good quality care according to the standards/ guidelines or best practices available for their condition, 45% of the respondents indicated this is not always the case. What is more, a shocking 74% of the respondents claimed their healthcare professionals did not ask for their feedback on the quality of care provided. These results are compelling because they depict a situation sadly too well-known for many patients in Europe: the lack of involvement in the whole journey of their treatment and care. EPF advocates for a meaningful involvement of patients at all stages of the healthcare's continuum, from diagnosis to treatment, and from treatment to rehabilitation/follow up.

A better relationship between patients and their healthcare professionals is pivotal in this regard. Thanks to the collaboration between patient organisations and healthcare professionals' and medical students' associations, we see an improvement in the relationship between patients and healthcare professionals. Patients are increasingly recognised as equal partner in the treatment decision system and this is echoed by the results of our survey: 84% of the respondents reported that they have been involved in the decision regarding healthcare and treatment by the healthcare professionals. This is encouraging and represents a welcome shift in the patient-doctor relationship.

The eye-opening results of our survey only reinforce our strong belief that there is still a lot to be done to achieve universal access for all in Europe. Via our campaign, and the work done with our members, EPF will continue to advocate for an ambitious action plan for EU and Member States to commit to, in order to achieve the ultimate goal of universal health coverage by 2030.

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

¹ http://www.eu-patient.eu/globalassets/policy/access/epf_position_defining_and_measuring_access_010316.pdf

The Importance of Involving Patient Organisations in Health Technology Assessment



Lydia MAKAROFF

Director, European Cancer Patient Coalition



Francesco FLORINDI

Head of EU Affairs, European Cancer Patient Coalition

Health technology assessment can be instrumental in delivering better treatments for patients. In Europe, the work done by the European Commission and the European network for Health Technology Assessment (EUnetHTA) has consolidated the role of health technology assessment, and promises to harmonise its impact across European countries. However, more work is needed to improve patient involvement in assessing new health technologies.

Patients must be involved in health technology assessment, so that the activities and decisions of assessment bodies have a greater focus on the people most directly affected by their decisions. People affected by serious diseases have unique knowledge, can contribute essential evidence, and have the same rights to contribute to health technology assessment as other stakeholders.

Today, very few health technology assessment agencies involve patients in their assessments, and the approaches vary when this engagement is sought. The level of influence and impact that patients have on decision-making is unclear, and may be limited. In some countries, health technology assessment publications may not be made publicly available, meaning that they cannot be scrutinised and challenged by patients and other stakeholders.

Barriers to involving patients in health technology assessment include a lack of established

methods for providing patient evidence, a lack of agreement on when patient engagement is needed, and a lack of capacity among all parties. Among European health technology assessment bodies, the National Institute for Health and Care Excellence in England (NICE) undertakes the most robust patient engagement scheme, although this does not guarantee access to valuable treatments.

Improving patient involvement in health technology assessment requires the processes for patient involvement to be defined through multi-stakeholder collaboration, and to be shared among European health technology assessment agencies. Health technology assessment agencies must be adequately resourced by Member States and trained in best practices for patient engagement. Patient organisations must also be supported by Member States, in order to increase their capacity to participate in health technology assessment.

The European Cancer Patient Coalition is a European umbrella non-governmental organisation that represents the interests of all cancer patient groups, from the most common to the rare forms of cancer. It represents over 400 Members in 46 countries. The European Cancer Patient Coalition supports transparency in health technology assessment processes and reimbursement decision-making, so that patients can scrutinise the decisions that affect them.

The European Cancer Patient Coalition's *Value of Innovation in Oncology* White Paper, launched in January 2017, provides the Coalition's policy positions on key obstacles to equitable access to meaningful innovation. It was written in collaboration with the Members of the European Cancer Patient Coalition, and contains recommendations for a more patient-centric health technology assessment process.

The European Cancer Patient Coalition recommends that:

- European and Member States decision-makers must define an ambitious political plan to continue harmonising health technology assessment at the European level.
- There should be a centralised, relative effectiveness assessment that is valid, binding and directly implemented in all European Member States and which considers patient-reported outcomes
- Patients and their representatives should be formally and routinely included in health technology assessment processes at European and national levels.

The European Cancer Patient Coalition continues to lead the campaign to support increased harmonization on health technology assessment across Europe, and for patients and their representatives to be formally and routinely included in health technology assessment policy and operations. Patients and patient organisations offer unique insights, identify unmet needs, and can help to produce practical recommendations to improve the health technology assessment process.

Increased transparency in development and pediatric medical research processes



Nessa CHILDERS

MEP (S&D), Member of the ENVI Committee

Children benefit from a regulatory environment which fosters the development of medicines to meet specific paediatric needs, but will benefit all the more from overall policies which are guided by the promotion of the interests of patients and public health.

Thus the European Parliament resolution of late 2016 on the regulation on paediatric medicines touches on the issue of limited market incentives to develop certain treatments. This applies to paediatric cancer just as well as to rare diseases. The former can take a rare form too, both can be fatal and the latter are not exclusive to adults either.

The scale and network gains which a common EU regulatory regime afford to the developers of pharmaceutical products certainly can and do facilitate the emergence of therapeutic options.

However, while this might tip the scales of the cost-benefit calculation in favour of development of new pharmaceutical treatment, it does not change the terms of the equation.

This requires public intervention to help meet unmet needs through funding, the facilitation of cross-border trials, or the provision and coordination of research by public and not for profit entities.

Such solutions may be in place but the political economy of pharmaceutical production is complex. The existing approaches do not guarantee a fair and equitable outcome between the pursuit of profit and the rightful expectation of access to the best healthcare provision we can potentially muster as a society.

Enabling trials across borders is a worthy goal and a commendable achievement but, to name an example of concern in the country I represent, it won't guarantee that children in Ireland who would qualify for compassionate use will get access to a treatment if a pool of trial patients is more easily reached on the continent.

Public funding for research can likewise fail to meet its potential to address unmet needs if its allocation is not adequately steered and incentives safeguarded from abuse.

In the same light, innovation can come in form rather than substance, be it to stretch intellectual property privilege or returns, so we cannot abandon critical sense to ensure that real improvements are reached in the race to provide hope to parents and patients, young and old.

Price increases and the depletion of public resources triggered by the financial crisis combined to confront European countries with challenges in the provision of healthcare once seen as matters of overseas development, rather than public policy at home.

But this might can help us look for solutions to serve the health needs of human populations across the globe start with similar steps, because some factors holding them back are the same.

We have made improvements in transparency of clinical trial data but pricing information is lacking. Public goods and public funding are involved, however, yet we struggle to even make sense of drug research and development costs.

Better access to information can help us shape incentives and could facilitate joint procurement.

Access to information can also contribute to access to treatment by allowing us to go beyond the logic of the markets where markets have not reached, and make them more equitable where they overreach.

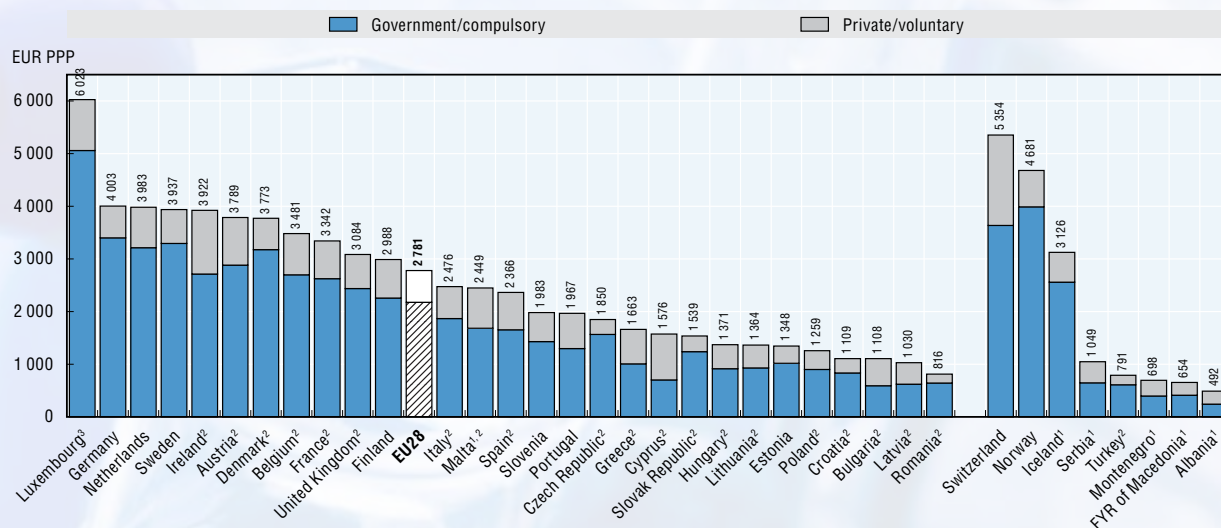
Public health policy exists to meet fundamental needs, and medicines markets are regulated accordingly, to govern the acquisition and reimbursement of drugs in our countries.

Likewise we have granted manufacturers intellectual property rights to exploit and spur advances in research. Transparent data should remind us that, more than an imperative, these rights are a means to an end.

They should be used and adjusted when - or to the extent that - they help us achieve our goals, together with other tools at our disposal, with innovation, access and affordability in mind.



Health expenditure per capita, 2015 (or nearest year)



1. Includes investments.

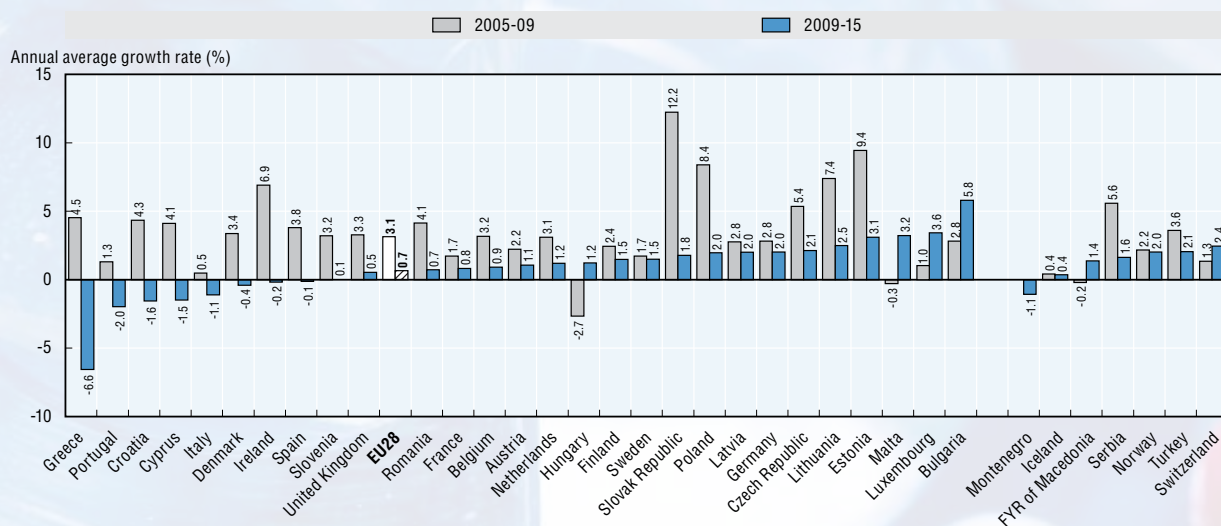
2. OECD estimate.

3. For Luxembourg, the population data refer only to the total insured resident population, which is somewhat lower than the total population.

Source: OECD Health Statistics 2016; Eurostat Database; WHO, Global Health Expenditure Database.

StatLink <http://dx.doi.org/10.1787/888933429236>

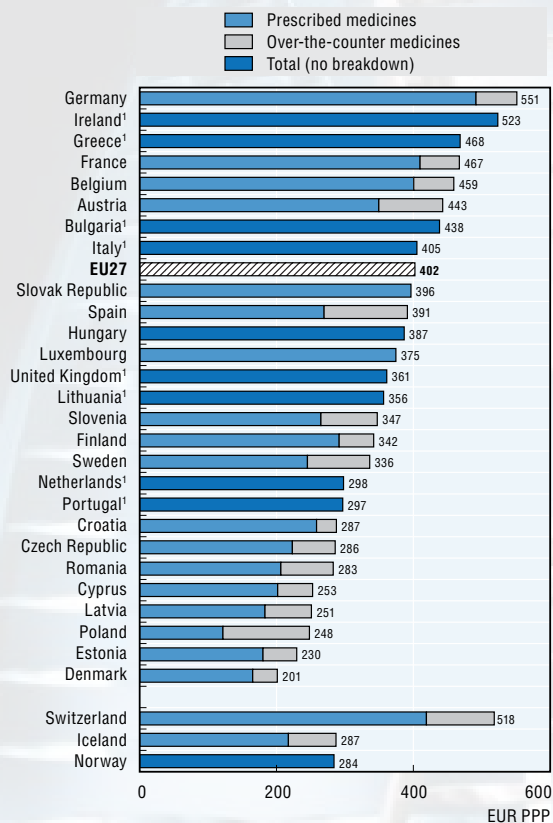
Annual average growth rate in per capita health expenditure, real terms, 2005 to 2015 (or nearest year)



Source: OECD Health Statistics 2016; Eurostat Database; WHO, Global Health Expenditure Database.

StatLink <http://dx.doi.org/10.1787/888933429242>

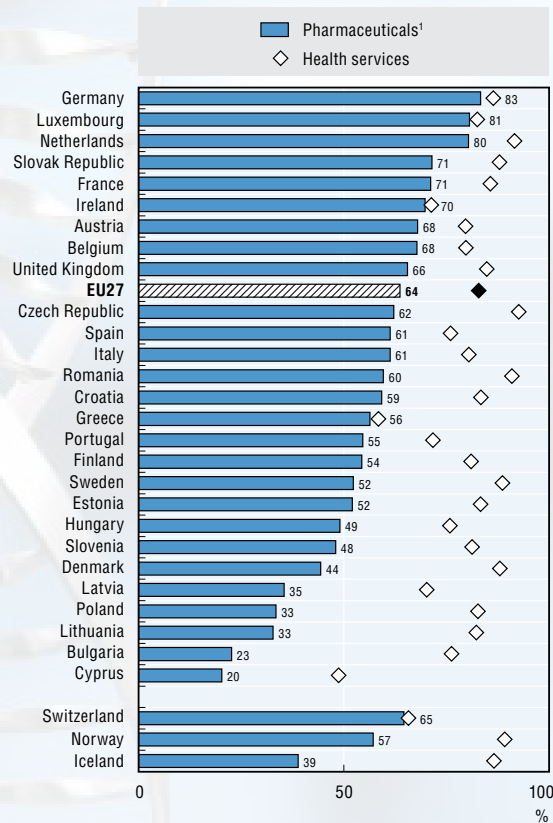
Expenditure on pharmaceuticals per capita, 2014 (or nearest year)



1. Includes medical non-durables.
Source: OECD Health Statistics 2016.

StatLink <http://dx.doi.org/10.1787/888933429302>

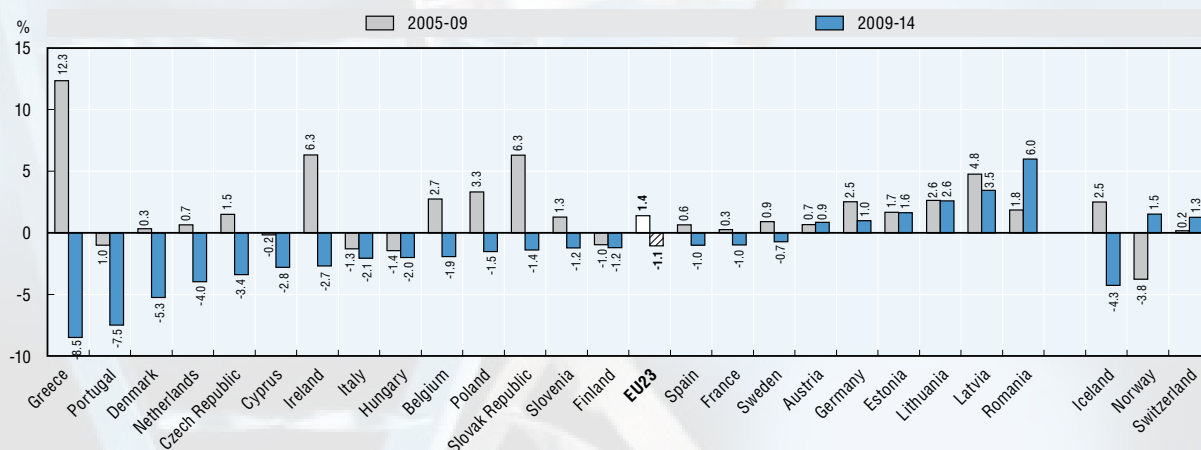
Public share of spending on pharmaceuticals compared with health services, 2014 (or nearest year)



1. Includes medical non-durables.
Source: OECD Health Statistics 2016.

StatLink <http://dx.doi.org/10.1787/888933429311>

Average annual growth in pharmaceutical expenditure¹ per capita, in real terms, 2005-09 and 2009-14 (or nearest year)



1. Includes medical non-durables.
Source: OECD Health Statistics 2016.

StatLink <http://dx.doi.org/10.1787/888933429320>

Incentive innovation and research in the medicines to boost the competitiveness



Patrizia TOIA

MEP (S&D), Vice-Chair of Committee on Industry, Research and Energy

Available European pharmaceutical industry is important for European public health, economic growth, trade and science. Research in new medicines contributes to health and quality of life of citizens by providing remedies to an increasing number of patients, through a more timely, widespread and equal access to pharmaceuticals. It is a matter of health of our citizens but also a matter of health of our economy. Healthcare sector and in particular pharmaceutical industry has an economic significance: the EU pharmaceutical sector accounts for around 1.8% of the total manufacturing workforce and is one of the industries with the highest labour productivity. Research-based pharmaceutical industry can play a critical role in restoring Europe's growth and ensuring future competitiveness in an advancing global economy. In 2015 it invested an estimated 31,500 million euro in R&D in Europe. It employs directly some 725,000 people and generates three to four times more employment indirectly than it does directly.

The innovative pharmaceutical industry is driven by, and drives, medical progress. It aims to turn fundamental research into innovative treatments that are widely available and accessible

to patients. As well as driving medical progress by researching, developing and bringing new medicines that improve health and quality of life for patients around the

world, the research-based pharmaceutical industry is a key asset of the Eu economy. It is one of Europe's top performing high-technology sectors.

However the global situation is evolving quickly. There is rapid growth in the market and research environment in emerging economies such as Brazil, China and India, leading to a gradual migration of economic and research activities from Europe to these fast-growing markets. In 2015 the Brazilian and Chinese markets grew by 14.0% and 7.0% respectively, compared with an average market growth of 5.9% for the total European market and 8.5% for the US market. The fragmentation of the EU pharmaceutical market has resulted in a lucrative parallel trade. This benefits neither social security nor patients and deprives the industry of additional resources to fund R&D. The European pharmaceutical industry serves as a major contributor to the EU's trading power. The EU was the world's major trader in medicinal and pharmaceutical products in 2013, with total trade amounting to 56.9 billion euro and the value of exports reaching more than 107.4 billion euro. Moreover the pharmaceutical industry is one of the cornerstones of a knowledge-based economy given the complexity of production processes and development as well as the nature of many new medicines. It is therefore essential for the EU to maintain its competitive edge, also to overcome the many challenges we have to face in the future. Demographic change is one of the key challenges the EU is facing. The number of EU residents aged 65 and over is expected to increase dramatically over the next 50 years, from 92 million in 2013 to 148 million in 2060. As health-related spending generally increases with the age of a person and the prevalence of chronic diseases like diabetes or dementia will rise with an ageing population, demographic transition is considered a major challenge for the financial sustainability of health and care systems. Public spending on health already accounts for more than 7% of GDP in the EU. By 2060 public expenditure on acute health care and long-term care measured as a percentage of GDP is expected to increase significantly (between 8.5 and 9.1% of GDP).

Nevertheless competitiveness in medicine research is often hampered by misuse of patent systems and by the high level of litigation cases aiming to delay generic entries. That's why we

need Eu-wide measures to guarantee the right of patients to universal, affordable, effective, safe and timely access to essential and innovative therapies, and to guarantee the sustainability of EU public health care systems. We need also EU-wide measures on the pharmaceutical market to reinforce the negotiation capacities of Member States in order to achieve fair prices for medicines. The Commission should promote open data in private research, especially where public funding is involved, and establish conditions such as affordable pricing and non-exclusivity, or co-ownership of IP for projects funded by EU public grants such as Horizon 2020. Together with Member States the Commission should also promote major publicly funded

investment in research based on medical needs, and introduce conditional funding based on affordable end pricing and non-exclusive licensing.



Access to Medicines at Sustainable Price: Pharma Industry and Governments Transforming Challenges into Opportunities



Jacek GLINKA

Interview of Jacek Glinka, President, Medicines for Europe

Healthcare systems under duress

In Europe today, healthcare systems are faced with budget cuts while the demand for treatment from an ageing population is increasing and the costs of providing access to new innovative medicines is rising. This is hardly a formula for healthcare sustainability. Governments have tried to address the gap between rising healthcare costs and limited healthcare budgets by drawing attention to lifestyle choices driving non-communicable disease and high prices charged by the originator pharmaceutical industry, but this approach has not resulted in a sustainable solution. What is missing from the government dialogue is a proposal of concrete measures to increase the efficiency of healthcare delivery. The absence of coherent policies to stimulate competition in the pharmaceutical market is a missed opportunity for governments and patients. Generic, biosimilar and value added medicines have demonstrated their incredible capacity to increase access to medicines across Europe in a financially responsible way. It is time for governments to agree on effective policies to support generic, biosimilar and value added medicines competition rather than continuing to employ short-sighted, cost-containment measures (such as mandatory price cuts in the off-patent sector, External Reference Pricing (ERP), tendering and payback/clawback policies), which endanger medicines supply reliability and ultimately patient health. With a renewed and coherent

policy to stimulate competition in the market, the medicines industry can help transform a challenge into an opportunity.

What is the contribution of the off-patent sector to healthcare sustainability?

In Europe the majority of prescriptions today are filled with generic medicines, although these medicines represent less than one quarter of total medicines costs, amounting to a mere 2-3% of total healthcare expenditure. As a result of generic medicines, patient access to high-quality essential medicines has doubled over the last ten years across Europe with no impact on treatment costs. Without generic medicines, European healthcare providers would have had to pay an additional €100 billion for medicines per year, according to IMS.

After only ten years, the availability of biosimilar medicines has also shown positive access trends for patients. For example, access to filgrastim, a biological treatment against neutropenia for cancer survivors, has increased across Europe by around 50% thanks to competition. In many countries the introduction of competitive biosimilar medicines has transformed the treatment options available to patients. With new biosimilar medicines on their way for therapeutic areas such as autoimmune diseases and cancer, it is anticipated that health systems will be able to deliver even greater access to biologic treatment at a sustainable cost.

Moving from a one-size-fits-all to a much more tailored and patient specific approach, value added medicines contribute to addressing unmet patient needs and are one of the key components of the customisation of healthcare. By answering patients' unmet needs, they represent a new horizon for those who are currently looking forward to a better quality of life with their treatment. Value added medicines are based on known molecules that address healthcare needs and deliver relevant improvement for patients, healthcare professionals and/or payers.

Recently, the Council Conclusions¹ underlined the importance of the timely availability of generic and biosimilar medicines to improve patient access to therapy and to ensure the sustainability of national health

systems. This now needs to be translated into policy action.

Can the off-patent industry do more for access and sustainability?

More should be done to increase the use of generic and biosimilar medicines for better access to medicines for patients without bankrupting healthcare budgets. The OECD¹, the European Commission^{2,3}, the European Parliament (INI report link here) and the European Council⁴ have all highlighted this as a priority for 2017 healthcare reform.

To fully realize the potential of generic and biosimilar medicines, the EU and member states should develop coherent policies to stimulate competition in the off-patent pharmaceutical market. Underlying economic and regulatory root causes contribute to unsustainable market conditions; these aspects are squarely within government authority to rapidly address. Specifically:

- Ensure predictable market environments for healthy competition
- Implement clear incentives to stimulate the use of generic and biosimilar medicines
- Improve regulatory efficiency to reduce administrative and cost burden of keeping products in the market
- Support manufacturing jobs in Europe with SPC manufacturing waiver
- Remove market barriers to allow generic and biosimilar medicines to compete from day 1 after patent expiry

<http://www.medicinesforeurope.com/news/european-health-ministers-call-for-more-competition-in-pharmaceutical-markets/>

1 OECD, Fiscal Sustainability of Health Systems: Bridging Health and Finance Perspectives, 2015

2 Investing in Health, 2013, DG SANCO, European Commission, http://ec.europa.eu/health/strategy/docs/swd_investing_in_health.pdf

3 DG ECFIN and Economic Policy Committee (Ageing Working Group), Joint Report on Health Care and Long-Term Care Systems & Fiscal Sustainability, 2016, http://ec.europa.eu/economy_finance/publications/eeip/ip037_en.htm

4 Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States - <http://www.consilium.europa.eu/en/press/press-releases/2016/06/17-epsco-conclusions-balance-pharmaceutical-system/>

What about access and affordability of medicines in the WHO European region



Zsuzsanna JAKAB

WHO Regional Director for Europe

In just over 50 years we have witnessed the change from a world of few medicines to an explosion of medicines to address infectious and non-infectious diseases, chronic diseases, orphan diseases, cancers and the new frontier of personalized medicine. However these innovations fail to realize their potential in improving health and alleviating suffering if there is not affordable and sustainable access to these innovations.

The WHO Regional Office for Europe has a unique window on these developments from a pan-European perspective and has contributed to the dialogue on sustainable access to medicines. In addition WHO has contributed to strengthening countries' pharmaceutical sector systems through technical advice on selection and responsible use of medicines, support to national regulatory authorities, the development or revision of national pharmaceutical policies, expanding the use of Health Technology Assessment (HTA), developing medicine pricing policies, and in new directions in procurement and supply chain management. For European Union member states there is an established system of regulatory harmonization. Many countries apply the principles of health technology assessment to support decision-making, clinical guidelines to support health care professional practice and widespread implementation of health insurance programs to try to manage costs and minimize the risks

of catastrophic health care expenditures for patients and their families. Yet there remain problems with affordable access and there are challenges with lack of transparency in pricing and, increasingly, unaffordable prices for new medicines.

In European countries that are not members of the European Union, these problems are magnified, facing the mix of significant fiscal constraints, limited public investment in health, weak regulatory systems, and frequently impoverishing out-of-pocket costs for patients. However, the demands for access to new innovative medicines remain. Access to Hepatitis C medicines illustrates the challenges – those countries with greatest need often have least capacity to provide an effective, curative treatment for affected citizens. Likewise, patients in resource-constrained environments want access to the same cancer treatments as their European counterparts. These realities challenge the principles of equality and solidarity that underpin regional activities and as reflected in the Health 2020 European policy for health and well-being.

The access to medicines agenda is recognized at the highest political levels. In November 2015, the Secretary-General of the United Nations, Ban Ki-moon, established the High-Level Panel on Access to Medicines, which delivered its final report in September 2016. The High-Level Panel drew particular attention to imbalances of power between institutions and inconsistencies between law, policy and practice with regard to the right to health, international trade and intellectual property law, and public health objectives and their effects on health technology innovation and access. Much work remains to be done to address these concerns.

WHO can contribute to new medicines development by identifying research gaps and needed medicines but cannot control nor finance this research agenda. Partnerships - like the Global Antibiotic Research and Development Partnership (GARDP) seeking more investment in research and development for new antibiotic treatments - have a key role to play. In addition, WHO just published a list of bacteria for which new antibiotics are urgently needed. Beyond priority setting and collaboration, it has been proposed there may

also be roles for WHO in coordinating currently fragmented international research by providing a forum for consultation and, with a strengthened capacity, to become a transparent source of reliable data on biomedical R&D, pricing, patent landscapes and clinical trials. (Burci and Goslin 2017)

The commercial and patient imperatives to bring new, effective medicines to the market quickly are obvious. What is less clear is how much the regulatory pathways can and should be adapted in order to support the earliest possible marketing authorization. Does early approval based on limited clinical trial experience and reliance on surrogate measures of treatment effect promote adoption of new expensive treatments that must inevitably come at the price of fewer funds available for other investments in health and social care?



There is evidence that the outcomes seen in clinical trials are often not replicated in real world use. What then for expensive new products of marginal benefit at the time of marketing authorization? Who should bear the costs of medicines that fail to deliver their promised benefits?

Equally troubling are reports of possible changes in the types and lower level of scientific rigour of evidence that might be accepted in support of marketing authorization. It is reported that the US 21st Century Cures Act, signed into law in December 2016, contains sweeping measures to permit manufacturers to submit less rigorous data to the FDA for approval of drugs and devices. (Kesselheim and Avorn 2017). The effects of this legislation and its reference to the promotion of “drug development tools” to facilitate new

drug approval need to be closely monitored to assess changes in the balance between innovation and access to markets, with public health objectives and responsible use of limited health care budgets.

The WHO Regional Office for Europe will continue to focus on promoting debate and facilitating Member State collaboration of important aspects of the access to medicines agenda. The WHO Regional Committee for Europe will consider at its meeting in September 2017 a proposal for country collaboration on horizon scanning, pricing and reimbursement and exchange of lessons learned and good practices. Successful collaboration and progress will depend on the political will of Member States.

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For the picture: <http://www.euro.who.int/en/about-us/regional-director/biography>



Should affordability come from the European legislator?



Karin KADENBACH

MEP (S&D), Member of the ENVI Committee

Speaking about affordability and sustainability in medicines, one should always think about the necessity of improving the access to the health care system to everybody, without borders or distinguishing between social classes. Ensuring that patients have access to essential and affordable medicines is one of the core objectives of the EU and the WHO.

After years of facing improvement, the economic crisis caused a worsening in patient access. The US and the European Union have now reached a problem, which has so far been relevant to poorer countries. Healthcare systems have been increasingly under pressure in recent years to accommodate an ageing population and growing demand for safe and effective treatments. We are facing increasing costs for our health systems amongst others due to high-priced drugs such as oncologics and new hepatitis C preparations. Innovative medicines often offer high-quality treatment, but are often extremely expensive and threaten the public health systems exorbitantly. In some cases, the price strategies of the pharmaceutical industry create financial barriers for the health systems, even in the richest countries in Europe.

The pharmaceutical industry is one of the most profitable industries in the world. Companies are generating high profits, mainly because pharmaceuticals are financed through

contributions from the compulsory insurance of the social health insurance companies as well as from taxes. Costs of research and development for innovative pharmaceutical and biological products are increasing. It takes an average of 12-13 years for a medicinal product to reach the market, posing a challenge for both payers and the pharmaceutical industry as they strive to provide patients with faster access to new, effective medicines. Nevertheless a right balance between a fair price for patients and a fair return on investment for industry should be the goal.

Faster access to innovative and affordable medicines, for the no profitable market of rare disease, is a matter of particular concern for me. Various factors influence the availability for orphan disease drugs, such as the selection of medicines on the market, the focus areas of pharmaceutical research, the supply systems, financing mechanisms, pricing, reimbursement and cost-containment policies of individual countries, as well as rigid patenting rules. Proper access means that all these factors should be properly analysed with the aim of finding ways of overcoming obstacles and reducing inequalities in access to medicines and treatments for patients. This is a priority for the S&D Group.

Everyone has a right to a good health care. That is why it is crucial that drugs are available to all citizens in the EU at a fair, reasonable and affordable price. For example, about 30,000 people are affected by hepatitis C, while 90,000 deaths can be prevented in Europe by

the use of modern, but expensive medicines. The European Parliament's Committee on Health (ENVI) is currently preparing an own-initiative report addressing obstacles to access to medicines and treatments and reducing inequalities. The EU must play a leading role in this important social challenge: from the safety control to efficacy, quality and accessibility of medicines. Transparency and independence of all stakeholders is indispensable.

Medical-based decision-making must acknowledge patient impact, not just price comparisons.

The pharmaceutical companies have a monopoly, especially through long-term patents. There is also a lack of transparency in terms of production costs. In particular, the rules at the international, European and national level make this possible. However, there will only be a change if the relevant rules are enforced and their compliance with the European institutions is strictly monitored. Negotiation should be transparent to avoid confidentiality agreements. A joint occurrence of the member States should be encouraged to strengthen the negotiating power, therefore leading to lower prices. Furthermore data gained through the developing process of the drugs, also so called negative data should be publicly available and access to data on all clinical trials carried out for new and existing medicines should be ensured. To avoid such obstacles we should increase public funding for innovative research and information on public funding of research and development should be available.



“Ensure that new treatments will reach patients equally in every corner of the EU”



Cristian BUSOI

MEP (EPP Group), Member of the ITRE Committee

In a 500 million citizen EU of 28 member states with an aging population and a higher prevalence of disease that drive a higher demand for healthcare, giving patients access to the best possible treatment available in Europe became a discussion about sustainability of healthcare systems, affordability of medicines or treatments, equity, quality and innovation in healthcare.

Despite all the efforts made by the EU in past few years and the progress made in health status and life expectancy, in the context of the economic and financial crisis affecting directly also healthcare budgets, there is still an unequal access to healthcare at EU level, and some of these inequalities are widening, not only across countries, but also across population groups within each country. Health inequalities usually result from the uneven distribution of social and environmental determinants; the differential access to resources such as education, employment, health services; different levels of participation in society and different levels of control over life. There is an evident difference between resource-limited Member States (Greece, Bulgaria, Romania, Portugal) and the wealth ones, such as Germany or UK. For these reasons, it is important to ensure that new treatments will reach patients equally in every corner of the EU.

We discuss more and more about revolutionary progress in health care sector, innovation in treatments and innovative medicines, as it has been proven they will enable us to live longer and better lives. For many European patients innovative treatments are the only hope to fight their disease – to give you a concrete example, over the past few years, immune therapies have dramatically changed the life of melanoma cancer patients, showing for the first time a durable survival rate and a good quality of life. The same significant progress has been shown in treating certain diseases that are now manageable chronic diseases as HIV or Hepatitis C, or in decreasing mortality in cancer.

But whether we can support innovation and afford it will depend on how health systems are and will allocate resources efficiently and sustainable, especially when national authorities have become increasingly concerned about affordability and sustainability issues, which should be clearly separated from each other.

Lately the discussion on affordability of medicines is always put together with “fair pricing” and the EU pricing mechanism. What does fair pricing means? From my point of view it means one that can reasonably be covered by patients and health budgets and simultaneously that continues to sustain research and development. Currently, high prices of many new medicines are challenging public health care systems or patients who have to pay for them out of pocket (as is the situation in most low- and middle-income countries). Although an EU price seems a rather simple and attractive solution on paper, its feasibility is rather challenging: not only is this a highly sensitive matter because of budgetary implications that Member States would like to keep control of, but given the differences in affordability across the EU, it is highly unlikely that a single EU price would be affordable for all EU countries. This would only be the case if the EU price would be the lowest common denominator across EU countries, which would have a significant impact on the ability of our pharmaceutical industry to generate sufficient resources that can be reinvested in R&D, therefore sustaining the virtuous circle of innovation. A differential pricing policy would allow taking into account the specificities of each country and their affordability levels

by enabling lower income countries grant patients access at a lower price

I believe that at EU level we should rather focus on ways to address the shortcomings of the current system, where there is a cross-border dimension and lay the ground for a differential pricing policy that would effectively contribute to higher affordability for lower income countries in the EU, particularly in Central Eastern Europe.

On the other hand when debating sustainability vs affordability, the real challenge for some Member States is the choice of short term affordability, despite the value of those therapies and their potential to generate savings in the long run. For such cases, when authorities have difficulties in covering the potentially high upfront investment, pragmatic affordability solutions need to be found and this should be done collaboratively, in cooperation with all actors of the healthcare system. This also requires a higher level of political willingness and acceptance, meaning also a certain degree of solidarity between EU Member States.

Although there may be areas where stronger cooperation can add value (e.g. early dialogue, therapeutic value assessments, horizon scanning, common registries etc.), it is highly unlikely that tackling pricing of medicines at EU level will deliver better affordability and patient access. Moreover the differences in the way healthcare systems are organized and financed, and that their clinical practice or epidemiology are often different, calls for solutions that are tailored to the specific situation of each country and each healthcare system, and last but not least pricing and reimbursement policies are a national competence and should remain so.

A positive agenda for better and affordable medicines in Europe



Yannis NATSIS

Policy Manager for Universal Access and Affordable Medicines, European Public Health Alliance (EPHA)

2016 is the year that political correctness went out the window when it comes to the debate on pharmaceuticals in Europe. The past year certainly marked a turning point and made clear that the problem of high prices of medicines is systemic and here to stay. As a sign of the critical times, the 28 European Health Ministers signed off the most strongly worded Council Conclusions ever. They broke a series of taboos and addressed the major shortcomings of the current pharmaceutical business model including the “holy grail”, the question of the overprotection, misuse and abuse of intellectual property incentives for medical innovation. In addition to the groundbreaking June 2016 Council Conclusions, the Belgian and Dutch HTA agencies commissioned the 6-month “Future Drug Pricing Scenarios” project which came forward with 4 alternative models of drug development, a solid response to the “there is no alternative argument”. Last September, the UN Secretary-General’s High-Level Panel report on access to medicines was published demonstrating that “the status quo is no longer an option” as The Lancet put it.

No more lip service

2017 started with equally comprehensive discussions in various fora such as the WHO Fair Pricing Forum, the OECD, the European Commission with the forthcoming proposal on HTA and last but not least, the European Parliament which recently adopted its position

on access to medicines. All of the above to say, that national and EU policy makers are aware of the problems and eagerly look for actionable solutions. Member states realise they have leverage towards drug manufacturers and are exploring paths how to use it. The voluntary intergovernmental collaboration initiative between the Netherlands, Belgium, Luxembourg and Austria, more commonly known as “Beneluxa” appears to be a game changer. Joint negotiations, international collaboration and more solidarity can effectively reduce information asymmetry and make it harder for the pharmaceutical industry to play the system.

The way forward

In terms of next steps, there needs to be systematic work on the tools we currently have such as the various pricing and reimbursement mechanisms but at the same time, we need to look at new tools and avoid piecemeal solutions. Public health leadership is essential and medical innovation incentives need to be tied to public health priorities. The evidence-based analysis mandated by the Council last June on the impact of the additional forms of patent protection (namely data, market exclusivities and the supplementary protection certificate) is a step in the right direction. The orphan drugs legislation put in place 17 years ago has given us some fantastic innovation but is more and more used for profit maximization by the industry to the detriment of patients. From the public health perspective, orphan drugs cannot be allowed to become the rule as they constitute an explosive mix of pared-down evaluations and the highest prices on the market. The same applies to the various early access schemes and the overall push for accelerated approvals embodied by the controversial adaptive pathways school of thought. Faster cannot be interpreted as easier because flexibility is important but so is patient safety. To this end, the further orphanisation of the pharmaceutical regulation must be avoided as that would hinder meaningful innovation and substantial therapeutic advance. That is why; the European Medicines Agency (EMA), the top EU regulator needs to send the right signals to the market namely that the so-called nichebuster business model is not sustainable. Speaking of the EMA, it is important to have a critical review of the regulator itself and

prevent further regulatory capture. What is the relationship between the EMA and the pharmaceutical industry when 83% of its funding is provided by those it is supposed to regulate? Are there sufficient checks and balances in place to ensure that there is no link between funding and decision-making? What can we learn from past mistakes to ensure they are not repeated?

Moreover, there needs to be more public funding into medical research and development (R&D). Public funds (in different shapes and forms) already play an important role and in certain therapeutic areas, they even exceed the private contribution. Hence it is critical to guarantee the public return on public investment with the appropriate public-interest conditionalities attached and the right governance structures in place. Europeans should not have to pay twice or even three times for their medicines since they already contribute to their development. This is particularly pertinent as the Innovative Medicines Initiative (IMI) and the post-Horizon 2020 era are reviewed.

The issue of healthy and robust competition is another critical area which can contribute to meaningful innovation and affordable treatments. Last but not least, the pursuit of transparency at all levels (in prices, in governance, in production and R&D costs, in the share of public funding, in clinical trials data to name a few) is of utmost importance. Experience teaches us that the secrecy and the policy fragmentation, two prevailing features of pharmaceutical decision-making, undermine governments’ leverage.

The political momentum around these issues will remain high during 2017 and 2018. The greatest challenge is for decision-makers to overcome the Stockholm Syndrome that a lot of those working on pharmaceuticals seem to collectively suffer from thinking that change is impossible. Besides, we need to keep in mind that most of the recent quite disruptive political developments briefly mentioned in this article were inconceivable only a few years ago. In other words, no solution or policy recommendation should be regarded as off-limits any longer.



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