REVIEWING ORPHAN DRUGS LAW: A TOUGH EQUATION

SPECIAL REPORT
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The Orphan Regulation was introduced in 2000 and its main objective was to address the challenge of regulating medicines which treat patients with rare diseases.

Around 30 million people suffer from such diseases across the EU.

In this Special Report, EURACTIV will try to analyse how the regulation has worked so far for different stakeholders involved as well as the implications of a potential review.
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The European Commission is expected to present by the end of July an evaluation study on the pros and cons of the application of orphan and paediatric regulations, which deal with a niche segment of rare diseases that affect fewer than five in 10,000 people.

The number of people who suffer from such diseases in the EU is around 30 million.

“Most patients suffer from even rarer diseases affecting one person in 100,000 or more,” the executive says.

The pharma industry has been reluctant to invest in medicines and treatments for patients with rare diseases because of the low commercial interest due to a comparatively small size of the market.

The Orphan Regulation introduced some incentives for the pharma industry to invest in these areas, which has brought so far, some positive results. The number of orphan medicines went from only eight products to more than 160 today while clinical trials increased by 88% between 2006-2016.

But now the Commission wants to re-open the legislation and make “corrections”, which critics suggest...
may prove to be risky for both the pharma industry and patients. The equation is tough to solve. Patients with rare diseases obviously want greater access to drugs, the pharma industry pushes for more incentives to invest in areas of unmet medical needs while governments want to save as much money as possible.

Sources have told EURACTIV that a legislative proposal to amend these regulations is due in late 2021 or early 2022. “The impact assessment of the legislative proposal has already started in the Commission,” the sources said.

OPENING PANDORA’S BOX?

An EU official told EURACTIV that the executive acknowledges a positive impact on the development of drugs for patients with rare diseases, including through financial incentives.

But the official pointed out there is still room for improvement, especially when it comes to the incentives, to enhance research on the 95% of rare diseases which still have no treatment options.

The official explained that the market situation cannot compare to 20 years ago, when the regulation took effect, but said that in some cases the ten-year market exclusivity may not be the most appropriate way to stimulate the development of new treatments for rare diseases.

Critics suggest, though, that shortening the timeframe of market exclusivity period has low added value in practice.

The reason is that the generics industry does not step in to produce generic orphan drugs because of their small market share and low profitability prospect.

The official also estimated the healthcare cost related to orphan medicines to have risen by €20-25 billion since 2000. But at the same time, this has resulted in significantly better health outcomes, meaning a better quality of life for patients.

INDUSTRY: THE REGULATION HAS BROUGHT RESULTS

For the pharma industry, the regulation has so far brought tangible results for patients and any attempt to change the incentives’ regulatory framework could produce unwanted counter-effects.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) says all healthcare stakeholders should work closely to ensure patients’ access to treatments.

“In addition, we need to further incentivise the research and development of new treatments for patients where, currently, no treatment options exist,” EFPIA said.

“EFPIA calls on European institutions to ensure a stable and predictable regulatory and incentives’ framework. This will support further research and development into much needed new treatments for rare diseases.”

According to the industry, 24 European Reference Networks have been established by 2018, while 23 European countries had developed national rare disease plans.

Another critical argument is that the orphan regulation has helped create 220 small- and medium-sized enterprises, which are responsible for the development of 51% of orphan medicines in Europe.

The debate over the issue is expected to heat up in the coming months, especially in light of the coronavirus pandemic and the industry’s efforts to come up with a vaccine against COVID-19 in record time.
EURORDIS: Rare diseases need more centralised processes within the EU

By Sarantis Michalopoulos | EURACTIV.com

Future improvement of the EU Orphan Medicines Regulation (OMP) could involve more centralised processes for all rare diseases at the EU level, the European Organisation for Rare Diseases (EURORDIS) told EURACTIV in a written interview.

“If there is already a lesson to be learnt by the current crisis we are all experiencing, is that a more functioning integrated Europe in health is needed when facing a common enemy,” EURORDIS said.

How do you evaluate the application of the EU Orphan Regulation so far?

The Regulation on Orphan Medicinal Products enshrined since 2000 the right for people affected by rare conditions to be entitled to the same quality of treatment as other patients. It has spearheaded common European work of great added value in rare diseases at large – in pooling of knowledge, in directing research funding, and in bringing into being innovative policies and systems.

The Regulation has been a success in fulfilling one of its primary purposes – to attract investment to the development of therapies for life-threatening or debilitating diseases for millions of people who today have either no treatment at all or no satisfactory treatment. For example, each year, 15% to 18% of new designations represent a first orphan product for its indication (rare diseases with no designated product ever before). 82% of authorised OMPs are new active substances, indicating a very innovation-oriented sector. 44% of all orphan products target a disease that has a prevalence of less than 1 in 10,000.

Unfortunately, this is not yet enough. The speed of research and quality of designation and applications should be improved. According to estimates by the Gianni Benzi Foundation, 23% of designated orphan products are later abandoned. Furthermore, we are witnessing a steady decline in the orphan designation since 2016. We cannot afford this: the vast majority of the 6,000 recognised rare diseases do not have a centrally authorised therapy.

We are also worried about some cases we have seen when existing, well established, and inexpensive hospital preparations for which there is no safety concern are repurposed into a product subject to marketing authorization, and that new product should then come at a price hundred
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At EURORDIS we are maturing our vision on what could be better legislation, better addressing the needs of people living with a rare disease and doctors, the interests of industry and the interest of payers.

Our ideas for future improvements to the OMP Regulation focuses on a reinforcement of the EU centralised processes in a structured and seamless way for all rare disease therapies. In particular, rare disease therapies – because of their very specific characteristics – do require a continuum of evidence generation, all through their life cycle, from scientific guidance and assessments until well after the moment of marketing authorisation.

Patients should be granted access to address the unmet needs of conditions which are frequently life-threatening and debilitating. We welcome the recent decision of the European Medicines Agency to waive fees for scientific advice to academics when investigating orphan products.

Our key concern prior to the pandemic was that the political environment didn’t feel ready to maintain or expand incentives: some Member States’ concerns on the sustainability of their healthcare budget are currently superior to their common objective of an EU agenda for knowledge, innovation, competitiveness and attractiveness in support of the needs of people with rare diseases. However, if there is already a lesson to be learnt by the current crisis we are all experiencing, is that a more functioning integrated Europe in health is needed when facing a common enemy.

Drug pricing has been a sensitive topic especially for rare diseases: What’s the best solution according to you, to ensure affordability and enable pharma innovation at the same time?

Our daily experience provides countless examples of situations when the price of a new orphan medicine proves to be the stumbling block on which manufacturers and payers fail to agree, with potentially dramatic consequences for the patients in need of access to therapies. We understand the multiple challenges policymakers and payers face, in an environment that is systematically failing patients. We call out the high price by default that we are seeing with little or next to no justification other than what the market is perceived to be able to bear, but there is also mistrust between payers and companies on the current economic model for orphan medicines.

EURORDIS has constantly tried to propose solutions to improve access to therapies for rare diseases, as well as increasing the number of therapies developed. In our Breaking the Access Deadlock to Leave No one Behind (2018) paper we expressed the ambition to have 3 to 5 times more new rare disease therapies approved per year by 2025, 3 to 5 times cheaper than today.

How? Amongst the four pillars we set out in that paper, we believe Europe has a great role to play to reduce the uncertainties that member states individually have when appraising therapies for rare diseases – pricing is one of the essential components.

Building on existing experiences and tools already available, such as cross-country (e.g. BeneluxAI) or European (on HTA for example) cooperation, we must link any discussion on the price with the level of evidence provided at the time of the negotiation and with clear post-marketing research activities towards the reduction of uncertainties.

Europe has the opportunity, with the forthcoming Pharmaceutical Strategy, to consider that a new ecosystem is possible, a framework based on a global approach to innovation for unmet medical needs and on sustainability for healthcare systems as well as financial attractiveness to industry and investors.

Do you have specific statistics/data on how many people managed to get treated/get therapy all this period of time?

As the number of orphan medicinal products approved centrally at the EU level has increased, so do the numbers of OMPs available in individual countries. Whilst authorisation is for the whole of the European Union, coverage is managed at the individual country, region, or even local hospital level. The accessibility for patients grows at an unequal pace across European countries. EURORDIS has carried out a number of surveys in the past, highlighting some of the issues that our community has experienced.

Results on patient experience of treatments from our latest Rare Diseases and Orphan Drugs Barometer survey (a quantitative survey, with over 7,500 respondents across the EU and world, presented at our European Conference on Rare Diseases and Orphan Drugs in May 2020) indicate that only 5% have already experienced a curative treatment, whilst 31% of respondents have never experienced any treatment for various reason – because there is no treatment, or they could not take part in the clinical trial, or the treatment is not affordable. We also observed a great variation of the number of treatments the patient could access depending on the disease area.

What could be improved in the EU legislation considering its upcoming review?

Times higher than that of the original preparation even though the approval remains based on a limited clinical data set, good manufacturing processes and toxicology studies. These practices are detrimental to both the accessibility of products to patients and the overall reputation of the industry working on making therapies available.

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EU orphan drugs law and the emergence of SMEs

By Sarantis Michalopoulos | EURACTIV.com

The legal framework provided by the current EU orphan drugs regulation has encouraged a number of small and medium-sized companies (SMEs) to develop innovative technologies in the fight against rare diseases in Europe, stakeholders have told EURACTIV.com.

The Orphan Regulation was introduced in 2000 and its main objective was to address the challenge of regulating medicines that treat patients with rare diseases. Around 246,000 people suffer from such diseases across the EU. The European Commission is expected to present by the end of July an evaluation study on the pros and cons of the application of orphan regulation.

EURACTIV understands that the executive wants to re-visit some terms of the regulation; however, patients and the pharma industry have voiced their concern about potential changes in the incentives’ regime, which could prove to be detrimental for innovation and research.

Pharmaceuticals have generally been reluctant to invest in rare disease treatments because of their limited commercial potential. Shortening the timeframe of market exclusivity period, for example, could further diminish the industry’s willingness to invest and thus leave patients stranded.

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On the other hand, public health systems across the bloc want to save as much money as possible while simultaneously protecting their population. Striking a happy balance will not be an easy task for the EU executive.

**A PERSONAL SME STORY**

Another aspect of this issue is the growing importance of SMEs, as some 220 pharmaceutical SMEs have sprung up, accounting for the development of 51% of orphan medicines in Europe.

One of those is Lysogene, a France-based phase 3 clinical-stage biopharmaceutical company focusing on treatments for rare paediatric neurodegenerative disorders with high and unmet medical needs.

The creation of the company in 2010 had a very personal touch: its founder and CEO, Karen Aiach, decided to launch her own company after her daughter Ornella was diagnosed with Sanfilippo syndrome type A, a devastating and deadly disease.

Aiach then abandoned her audit specialist career and started her own company to tackle this highly unmet medical need.

In the beginning, she invested her savings and managed to attract the attention of several venture capital firms and investment banks.

The company has so far succeeded in developing a polyvalent technology platform broadly applicable to central nervous system diseases and building up relations with academic centres, key opinion leaders and patient groups around the world.

“The EU Orphan Regulation is particularly beneficial for SMEs developing orphan drugs (OMP-SMEs), like us, due to the financial incentives, support from agencies and patient access,” Lysogene said in an emailed response.

The company said OMP-SMEs are in general more vulnerable to economic failure than companies with a broader portfolio and the EU orphan law has been helpful.

“The Regulation supports SMEs by encouraging them to develop technologies, innovation and gain expertise which can often apply or be adapted to other rare diseases,” the company said.

“It has definitely helped SMEs to explore ‘niche’ areas as it increases the focus on rare diseases and provides SMEs with some interesting incentives. It also contributes to an increase in basic research projects in rare diseases which can be developed in collaboration with SMEs or from which SMEs can emerge,” the company added.

**INCENTIVISING SMES**

For Lysogene, the Orphan Regulation has helped some SMEs flourish thanks to a number of tools it provides.

“The public announcement of orphan drug status has a positive effect on investors; it demonstrates robust proof of concept and a product’s potential endorsed by key regulators,” the company said, adding that access to H2020 funding programme is also granted.

The company said the direct financial incentives linked to the orphan status enable SMEs to access procedures at the European Medicines Agency (EMA) that would otherwise have a cost.

“We benefited from fee reductions for scientific advice procedures, whose cost ranges between €22 and €90k, with a 75% reduction for orphan products that can reach 100% if paediatric-related questions are discussed during the scientific advice.”

Moreover, fees of additional procedures with EMA are waived when the company is also an SME.

“This allows us to seek advice on our products’ development on a regular basis without being blocked by the potential cost of these procedures,” Lysogene said, adding that the EU orphan regulation also allows SMEs to receive additional advice and support from agencies specific to orphan products and their associated challenges.

“The orphan status gives us access to protocol assistance, a scientific advice procedure focusing on challenges of product development in rare diseases.”

**STILL A CHALLENGING ENVIRONMENT**

EURACTIV also contacted the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), which said the environment of rare diseases is very challenging for smaller companies.

“Most of them are far from making a profit and they re-invest in very risky R&D. It is vital not to strangle them to keep competition in the field,” EUCOPE warned.

The association added that although the regulation has helped foster the development of OMPs, the competitiveness in Europe is decreasing and might lead to postponing innovation, especially in the rare diseases area.

“The EU simply cannot afford this innovation blackhole.”

EUCOPE explained that a lesson to be learnt from the pandemic is that “where there is a will, there is a way”. “The potential of digital to bring together clinical trial data for rare diseases for instance – needs to be used post-crisis for rare diseases.”
When it comes to rare diseases and ‘orphan drugs’, technology is there to support an “objective” EU tool that could provide the pharma industry with the necessary incentives to research and produce orphan drugs and simultaneously avoid exhausting ailing health systems, MEP Stelios Kypouropoulos told EURACTIV in an interview.

This tool, according to Kypouropoulos, will not allow unnecessary price fluctuations and will ensure the best price for each member state separately in order for orphan drugs to be granted to patients at the right price for national health systems.

“This will maintain the incentive to continue production and research for pharmaceutical companies and on the other hand, will help health systems afford orphan drugs,” he said.

The Orphan Regulation was introduced in 2000 and its main objective was to address the challenge of regulating medicines that treat patients with rare diseases, i.e. those that affect fewer than five in 10,000 people.

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All relevant stakeholders acknowledge the added value of the regulation when it comes to the production of new orphan drugs, but the European Commission now wants to re-visit parts of the legislation.

For the pharma industry, touching the incentives could harm innovation and limit much-needed access to therapies for patients.

EU member states, on the other hand, prioritise the sustainability of their healthcare systems and therefore seek the lowest price possible.

**THE REGULATION HAS WORKED**

An evaluation study on the pros and cons regulation is due at the end of July.

An EU official recently told EURACTIV that orphan drugs have cost EU health systems an additional €20-25 billion between 2000-2017 but at the same time, between 210,000-440,000 ‘quality-adjusted life years’ were gained to the benefit of patients.

The term quality-adjusted life years expresses the additional number of years which a person lives as a result of receiving a treatment, taking into account the quality of life in those years.

Kyproupooulos said the regulation has brought remarkable results so far.

“168 innovative drugs have been made available to patients with a rare disease, improving the health and therefore the quality of life of thousands of people,” the European People’s Party (EPP) MEP said.

“Businesses, on the other hand, seek legal security and stability to make financial investments, and this Regulation offers this, bringing many drugs to our domestic market. And that’s the bottom line, existing treatments to be available to everyone.”

However, he said, improvements are needed, especially in terms of European funding and opportunities given to start-ups, small and established companies to build their know-how on the development and distribution of new drugs.

“In order to develop innovation and maintain it within the EU, economic incentives should be given to researchers, but also at the European Commission level, research should be a priority for future goals,” the MEP said.

“At universities, working with research centres, civil society and businesses can help shape a curriculum that is up-to-date and future-oriented,” he emphasised.

**LESSONS LEARNT FROM COVID-19**

Referring to the lessons learnt from the ongoing COVID-19 pandemic, the Greek MEP said there is enormous room for improving European coordination.

“Europe's main goal is to preserve health for all. As an MEP and doctor, I am proud to serve this purpose,” he said, adding that investment in research and a unified way of distributing medicines to all member states is an area that the EU needs to target even more.

He emphasised that policies, parties and different working committees intersect at some point.

“The European Union has civil society at its core and to maintain this heritage, it must offer prosperity. One way to do this is through medication for all, even with Orphan Medicines,” he concluded.
L
ivening through a global pandemic, we can take some comfort from the enormous collaborative research and development response that is taking place to find a way out from under the shadow of the COVID-19 crisis. Scientists around the world are working to find new diagnostics, treatments and vaccines to use in the fight against the coronavirus.

Nathalie Moll is the Director General of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

The polar opposite of a pandemic, a rare disease may only affect a handful of patients in a particular country, but to the patient, their family, carers and clinicians, the impact of their condition can be just as devastating. Often genetic, discovered in childhood and frequently severe, rare diseases are some of the most significant scientific challenges in medicine. Typically they affect only 1 in 2,000 people, but there are more than 6000 rare diseases meaning around 30 million Europeans are living with some form of rare condition.

Rare diseases certainly don’t attract the levels of media attention and

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interest that a public health crisis like COVID-19 does but for patients living with the 95% of rare diseases where no treatment options exist, the need for new diagnostics and medicines is every bit as real.

As the industry responsible for developing those new therapies, we are committed to achieving the crucial objective of finding new treatments for patients in areas of unmet medical need. It means supporting and strengthening the framework of incentives to drive further research into the next generation of treatments and cures for rare disease and paediatric treatments. Incentives drive investment, research and results. Results that mean new treatments and ultimately better outcomes for patients.

It is why EFPIA supports the existing European legislation on orphan medicines and paediatric medicines, while underlining the need to co-create vehicles to address issues around access to new treatments. Prior to the orphan legislation coming into force in 2000, there were just 8 treatments licensed for use to treat rare diseases, now there are 169, underlining the fundamental role that a predictable and stable incentives framework for research and development has. Any destabilisation of that framework threatens the investment in research and development in this area.

At the same time, faster, more equitable access to new rare disease treatments for patients across Europe is a shared goal and responsibility. Re-opening the Orphan Medicinal Product Regulation will not address the core challenges regarding unequal access and availability of orphan drugs within the European Union. Addressing this challenge requires a structured dialogue with relevant stakeholders, Member States and the European Commission sensitive to their respective competence areas, to find solutions to introduce these ground-breaking treatments. That is why we reiterate the call to Member States and the Commission to set up a High-Level Forum composed of EU and national decision makers, patients, as well as the research and healthcare communities to find collaborative, multi-stakeholder solutions to these complex issues of access.

Considering the lack of innovation policy drivers in the Roadmap for the EU's Pharmaceutical Strategy, it is all the more critical that we maintain a stable and predictable incentives framework that can continue to support the development of new treatments for rare disease patients in Europe. We have to work together to ensure access to new treatments and technologies today, medical innovation in rare diseases for tomorrow and sustainable healthcare systems in a globally competitive Europe. Destabilising investment in the discovery and development of new treatments for patients living with rare diseases by re-opening a legislation, proven to be effective in stimulating the development of new treatments, cannot be the right approach.

One crystal clear lesson from the COVID-19 pandemic has been that the answer lies in medical innovation. This is equally true for patients living with rare diseases. Now is the time to re-build and re-energize rather than devalue Europe’s health research ecosystem, to make sure we address these challenges and #WeWontRest until we make treatments for rare diseases less rare.

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There are multiple challenges inherent to drug development for rare diseases, all consequences of the small number of patients. For most of these diseases, the body of pre-existing knowledge is extremely limited with a lack of crucial information such as its determining factors, since in most of the cases there are no consolidated outcome measures to assess clinically meaningful improvements.

Diego Ardigò is the Head of Global Rare Diseases, Research & Development at Chiesi.

This absence of background information on the disease impacts the foundational knowledge upon which the clinical development of new drugs is based. Besides the need to generate from scratch a relevant amount of observational data, this lack of information significantly increases the risk of producing incomplete or inconsistent results in clinical trials. In addition, the size and utility of observational and investigational studies is severely impacted by the difficulty (sometimes even the impossibility) of recruiting a sufficient number of patients to obtain fully-powered and informative results.

Sometimes even the diagnosis of the disease is an undefined and intricate process. The identification of patients and their subsequent referral to treatment centers (or network of centers) is now increasing, thanks to the efforts of the European Reference Networks and some influential patient associations, but most patients are still not diagnosed or are unknown to the specialized medical community. This makes the patient journey a long and arduous experience with an unpredictable outcome even when safe and effective treatments are available.

Finally, the costs incurred in rare disease development could be less than those of products targeting large populations, but are still highly significant and should by no means be minimized: the quality and non-clinical development is largely independent from the size of patient pool and the clinical studies might be smaller than those of mass market drugs but the cost-per-patient is orders of magnitude greater. In these conditions, the risk of financial unsustainability is high for developers in the absence of incentives and compensation systems. This is particularly true for ultra-orphan conditions where there are only several hundred or fewer of patients, globally.

How are R&D decisions are taken?
Based on what criteria?

In general, drug development decisions are based on the possibility to fulfill significant medical/patient

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needs (i.e. whether a new drug is meaningful to patients and to the health care system), on being able to demonstrate this relevant benefit through clinical trials (i.e. whether a new drug generates compelling clinical data), and considering the complexity and challenges and risks of investment in R&D and manufacturing.

This general framework is true also for rare diseases, with greater risks and uncertainties related to the viability due to the disproportionately lower number of patients to be treated in the future commercial setting compared to the costs and risks. Over the years, an increased pressure on industry has arisen to develop new treatments for a limited number of rare diseases, characterized by a manageable balance between up-front costs and possibility of future, although highly uncertain, returns.

The existing incentives for orphan drug development, as well as the progressive evolution of the regulatory system toward a sensible flexibility, have helped industrial sponsors maintain the possibility of developing new drugs for rare disease characterized by relevant medical needs. Legislative or policy changes that lead to a less favourable balance between inherent risks and future potential returns will likely move the decisions of pharmaceutical companies away from rare diseases.

**Do you feel that the industrial strategy and the expected pharmaceutical strategy will have a positive or negative effect on the industry? Where do you see opportunities and potential risks?**

The renewed industrial strategy and the expected pharmaceutical strategy are a landmark opportunity to ensure that the European life science industry will be able to compete at a global level, while ensuring access to innovative treatments to European patients. On the strategy itself, the renewed commitment to strengthen smart IP policies is a very positive, necessary, message. The pharmaceutical strategy would be a chance to open a constructive discussion on how we can strengthen the competitiveness of our regulatory framework: making it fast, flexible, and effective, so that it will deliver both safe and efficacious products to patients as well as attract innovative developers. This is a key driver when it comes to deciding where to carry out R&D activities at global level—an area where Europe has constantly lost ground in the last 20 years.

We think that whatever strategy is proposed it should aim to benefit people living with diseases, and this means incentivising research rather than merely focusing on increasing manufacturing capacity.

**The success of the orphan regulation is widely recognised. However, EU member states worry about pricing issues and lack of investment in certain areas where there is unmet medical need. How would you respond to these? How can they be addressed if not by amending the regulation?**

For society to work well, we believe it is important that a serious, clear and continual dialogue is maintained across different stakeholders, while respecting their own competencies. Everyone has their own role to play, and ultimately everyone should ensure that their actions generate societal benefits.

To this end, mixing pricing concerns with R&D incentives and related regulations lead to a very dangerous path that can be really detrimental for EU patients and EU pharmaceutical R&D operations. As a mid-size European pharmaceutical group operating at a global level with a strong commitment in the rare diseases area, we hope that the new EU mandate will aim at maintaining incentives to ensure a proper level of investment for areas of high unmet need, as is the case for ultra-orphan conditions where traditional business models don’t apply. On the access front, we fully understand that it is not acceptable to have a European Union that operates at different speeds when it comes to access to treatments. That’s why we think that it is time to reflect with all stakeholders on new models to finance innovation to ensure access for all EU patients and drive sustainability for health systems.

At a societal level, the impact of the cost of orphan drugs is limited, and will continue to be so when compared to treatments for much bigger patient populations. Many other components of healthcare systems spending are significantly more inefficient than the 5% of total pharmaceutical expenditure devoted to rare disease drugs in the EU.

Finally, a continued focus on pricing by European authorities rather than the still very high need to incentivise research will likely push companies to other geographies such as the US and emerging countries, leaving the European patients at a net loss. This, we believe, is also a net loss for the European society, as it will likely induce European companies to intensify their activities (on research, clinical development, formulation development, commercialization) away from Europe.